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L86  ANSWER 1 OF 86  HCAPLUS  COPYRIGHT 2001 ACS
AN   2001:31741  HCAPLUS
DN   134:80804
TI   Cyclotron mass spectrometry screening
IN   Raillard, Sun Ai; Stemmer, Willem P. C.; Patten, Phillip
     A.
PA   Maxygen, Inc., USA
SO   PCT Int. Appl., 52 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE          APPLICATION NO.  DATE
     ---------------    ----  --------      ---------------  --------
PI   WO 2001002865      A1    20010111      WO 2000-US18450  20000705
         W:  AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,
             CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
             IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
             MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
             SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
             CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRAI US 1999-142478   19990706
AB   Methods and integrated systems for performing cyclotron mass
     spectrometry-based screening of large libraries are provided.  The
     methods, app., and integrated systems are adapted to screening libraries
     of compds. in vivo and in vitro.
RE.CNT  4
RE
(1) Anon; 1997, 7, HCAPLUS
(2) Anon; 1998, 23, HCAPLUS
(3) Fang, A; COMBINATORIAL CHEMISTRY AND HIGH THROUGHPUT SCREENING 1998, V1(1),
    P23 HCAPLUS
(4) Nawrocki, J; RAPID COMMUNICATIONS IN MASS SPECTROMETRY 1996, V10(14), P1860
```

HCAPLUS

L86 ANSWER 2 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2001:12294 HCAPLUS
DN 134:76367
TI Methods and compositions for engineering of attenuated vaccines
IN Punnonen, Juha; Howard, Russel; **Stemmer, Willem P. C.**; **Delcardayre, Stephen**; Apt, Doris
PA Maxygen, Inc., USA
SO PCT Int. Appl., 119 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001000234	A2	20010104	WO 2000-US16984	20000620

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-344655 19990625
AB This invention provides attenuated vaccines, and methods of obtaining attenuated vaccines. The vaccines of the invention include recombinant viral, bacterial, parasite, and other organisms that are evolved to exhibit increased attenuation without loss of effectiveness as a vaccine. The methods involve the creation of libraries of recombinant nucleic acids (e.g., whole or partial genomes, or particular nucleic acids) which are introduced into the vaccine viruses or other organisms, followed by screening and/or selection for those viruses or organisms that are attenuated.

L86 ANSWER 3 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:887333 HCAPLUS
TI Breeding of retroviruses by DNA **shuffling** for improved stability and processing yields
AU Powell, Sharon K.; Kaloss, Michele A.; Pinkstaff, Anne; McKee, Rebecca; Burimski, Irina; Pensiero, Michael; Otto, Edward; **Stemmer, Willem P. C.**; Soong, Nay-Wei
CS Genetic Therapy Inc., Gaithersburg, MD, 20878, USA
SO Nat. Biotechnol. (2000), 18(12), 1279-1282
CODEN: NABIF9; ISSN: 1087-0156
PB Nature America Inc.
DT Journal
LA English
AB Manufg. of retroviral vectors for gene therapy is complicated by the sensitivity of these viruses to stress forces during purifn. and concn. To isolate viruses that are resistant to these manufg. processes, we performed breeding of six ecotropic murine leukemia virus (MLV) strains by DNA **shuffling**. The envelope regions were **shuffled** to generate a recombinant library of 5 .times. 106 replication-competent retroviruses. This library was subjected to the concn. process three consecutive times, with amplification of the surviving viruses after each cycle. Several viral clones with greatly improved stabilities were isolated, with the best clone exhibiting no loss in titer under conditions that reduced the titers of the parental viruses by 30- to 100-fold. The envelopes of these resistant viruses differed in DNA and protein sequence, and all were complex chimeras derived from multiple parents. These studies demonstrate the utility of DNA **shuffling** in breeding viral strains with improved characteristics for gene therapy.
RE.CNT 20

RE
(2) Bae, Y; J Virol 1997, V71, P2092 HCAPLUS
(3) Braas, G; Bioseparation 1996, V6, P211 HCAPLUS
(4) Burns, J; Proc Natl Acad Sci USA 1993, V90, P8033 HCAPLUS
(5) Crameri, A; Nature 1998, V391, P288 HCAPLUS
(7) Fass, D; Curr Biol 1995, V5, P1377 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 4 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:842812 HCAPLUS
DN 134:110987
TI Molecular breeding: the natural approach to protein design
AU Ness, Jon E.; **Del Cardayre, Stephen B.**; **Minshull, Jeremy**; **Stemmer, Willem P. C.**
CS Maxygen, Redwood City, CA, 94063, USA
SO Adv. Protein Chem. (2001), Volume Date 2000, 55(Evolutionary Protein Design), 261-292
CODEN: APCHA2; ISSN: 0065-3233
PB Academic Press
DT Journal; General Review
LA English
AB A review with 112 refs. is presented regarding mol. breeding which allows protein engineers to homologously combine multiple related genes by a process that closely mimics sexual recombination to generate functional diverse libraries of chimeric proteins from which improved variants can be selected. (c) 2001 Academic Press.
RE.CNT 110
RE
(1) Arkin, A; Bio/technology 1992, V10, P297 HCAPLUS
(2) Arnold, F; Acc Chem Res 1998, V31, P125 HCAPLUS
(3) Arnold, F; Nature Biotechnology 1998, V16, P617 HCAPLUS
(4) Arnold, G; Biophys J 1997, V73, P1147 HCAPLUS
(5) Babbitt, P; Science 1995, V267(5201), P1159 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 5 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:833548 HCAPLUS
DN 134:13986
TI Recombination of polynucleotide sequences using random or defined primers and staggered extension
IN Arnold, Frances H.; Shao, Zhixin; Affholter, Joseph A.; Zhao, Huimin H.; **Giver, Lorraine J.**
PA California Institute of Technology, USA
SO U.S., 40 pp., Cont.-in-part of U.S. Ser. No. 905,058, abandoned.
CODEN: USXXAM
DT **Patent**
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6153410	A	20001128	US 1997-905359	19970804
	WO 9842728	A1	19981001	WO 1998-US5814	19980325
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	WO 9842832	A1	19981001	WO 1998-US5956	19980325
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

	AU 9867725	A1	19981020	AU 1998-67725	19980325
	AU 9869420	A1	19981020	AU 1998-69420	19980325
	AU 724698	B2	20000928		
	EP 920496	A1	19990609	EP 1998-915171	19980325
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	BR 9804791	A	19990817	BR 1998-4791	19980325
	EP 975653	A1	20000202	EP 1998-913096	19980325
	R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE, PT, IE, FI				
	JP 2000511783	T2	20000912	JP 1998-545987	19980325
	US 6177263	B1	20010123	US 1999-353556	19990714
PRAI	US 1997-41666	19970325			
	US 1997-45211	19970430			
	US 1997-46256	19970512			
	US 1997-905058	19970801			
	US 1997-905359	19970804			
	WO 1998-US5814	19980325			
	WO 1998-US5956	19980325			

AB A method for in vitro mutagenesis and recombination of polynucleotide sequences based on polymerase-catalyzed extension of primer oligonucleotides is disclosed. The method involves priming template polynucleotide(s) with random-sequences or defined-sequence primers to generate a pool of short DNA fragments with a low level of point mutations. The DNA fragments are subjected to denaturization followed by annealing and further enzyme-catalyzed DNA polymn. This procedure is repeated a sufficient no. of times to produce full-length genes which comprise mutants of the original template polynucleotides. These genes can be further amplified by the polymerase chain reaction and cloned into a vector for expression of the encoded proteins. This method was applied to the prodn. of mutants of Bacillus subtilis subtilisin E, B. subtilis p-nitrobenzyl esterase, and Actinoplanes utahensis echinocandin B deacylase.

RE.CNT 66
RE
(2) Anon; WO 9517413 HCAPLUS
(3) Anon; EP 0252666 1988 HCAPLUS
(4) Anon; WO 9007576 1990 HCAPLUS
(5) Anon; WO 9014430 1990 HCAPLUS
(6) Anon; WO 9101087 1991 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 6 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:742226 HCAPLUS
DN 133:291931
TI Modified starch metabolism enzymes and encoding genes for improvement and optimization of plant phenotypes
IN **Stemmer, Willem P. C.**; Subramanian, Venkitswaran; Raillard, Sun Ai; Huisman, Gjalt
PA Maxygen, Inc., USA
SO PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000061731	A2	20001019	WO 2000-US9840	20000412
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-129009 19990413

AB The invention provides methods for generating, identifying, and selecting polynucleotides encoding novel starch metabolizing enzymes (NSME), NSME-encoding polynucleotides, compns. of recombinant **shuffled** NSME protein, plant cells and microbes contg. a **shuffled** NSME polynucleotide in expressible form, plants contg. a **shuffled** NSME polynucleotide in expressible form, novel starch compns. produced by said plants and cells, uses of such plants, cells, and starch compns. Thus, to create an ADP-glucose pyrophosphorylase with altered properties, the genes from E. coli and other microorganisms which have at least 70% sequence identity are randomly fragmented with DNase I and fragments of 100-300 bp are selected. These fragments are reassembled based on sequence similarity by primerless PCR. Recombination as well as variable levels of mutations that are introduced by the PCR reaction to generate the diversity. The assembled genes are cloned into a starch minus E. coli mutant that lacks the NSME. Transformed colonies expressing a functional NSME are screened for prodn. of glycogen by iodine staining. Those colonies staining dark blue are presumed to contain deregulated NSME. Colonies expressing **shuffled** NSME genes are selected and grown in larger amts. in liq. culture and assayed for specific properties. Genes from those clones expressing one or more of the desired properties are iteratively **shuffled** in order to achieve optimization of one or more of the desired properties. The optimized gene is used to transform the desired crop plant in order to deregulate and increase starch biosynthesis in various tissues including tubers and seeds.

L86 ANSWER 7 OF 86 HCAPLUS COPYRIGHT 2001 ACS

AN 2000:736184 HCAPLUS

DN 133:291923

TI Methods of **shuffling** polynucleotides by fragmentation and multi-cyclic extension

IN **Stemmer, Willem P. C.**

PA Maxygen, Inc., USA

SO U.S., 61 pp.
CODEN: USXXAM

DT **Patent**

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6132970	A	20001017	US 1998-100856	19980619

AB The invention is directed to methods of **shuffling** polynucleotide variants. The methods entail conducting a multi-cyclic polynucleotide extension process on partially annealed polynucleotide strands having sequences from the plurality of chosen polynucleotide variants, the polynucleotide strands having regions of similarity and regions of heterol. with each other and being partially annealed through the regions of similarity, under conditions whereby one strand serves as a template for extension of another strand with which it is partially annealed to generate a population of **shuffled** polynucleotides. **Shuffled** polynucleotides are then selected or screened to identify a **shuffled** polynucleotide having a desired functional property. The DNA **shuffling** method, when applied to the TEM-1 .beta.-lactamase gene, yielded a mutant with a 16,000-fold increased resistance to cefotaxime (MIC = 0.02 .mu.g/mL to MIC = 320 .mu.g/mL). The method was also exemplified by (1) **shuffling** the murine and human interleukin-1.beta. genes, (2) LacZ alpha gene reassembly, (3) improvement of antibody ALOB by DNA **shuffling** of a library of all 6 mutant CDRs, and (4) multiple cycles of interplastidic direct repeat recombination.

RE.CNT 60

RE

(1) Anon; EP 552266 HCAPLUS

(2) Anon; EP 0252666 B1 1988 HCAPLUS
(3) Anon; WO 9007576 1990 HCAPLUS
(4) Anon; WO 9014424 1990 HCAPLUS
(5) Anon; WO 9014430 1990 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 8 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:639148 HCAPLUS
DN 133:233552
TI Methods for generating polynucleotides having desired characteristics by iterative selection and recombination
IN **Stemmer, Willem P. C.**
PA Maxygen, Inc., USA
SO U.S., 106 pp., Cont.-in-part of U.S. 5,811,238.
CODEN: USXXAM
DT **Patent**
LA English
FAN.CNT 8

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6117679	A	20000912	US 1996-621859	19960325
	US 5811238	A	19980922	US 1995-564955	19951130
	US 5837458	A	19981117	US 1996-650400	19960520
	CA 2239099	AA	19970605	CA 1996-2239099	19961202
	WO 9720078	A1	19970605	WO 1996-US19256	19961202
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9710873	A1	19970619	AU 1997-10873	19961202
	AU 713952	B2	19991216		
	EP 876509	A1	19981111	EP 1996-940934	19961202
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	EP 911396	A2	19990428	EP 1998-122014	19961202
	EP 911396	A3	19990506		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2000500981	T2	20000202	JP 1997-520744	19961202
	JP 2000308490	A2	20001107	JP 1999-267847	19961202
	WO 9735966	A1	19971002	WO 1997-US4715	19970320
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, US, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9725426	A1	19971017	AU 1997-25426	19970320
	EP 906418	A1	19990407	EP 1997-916943	19970320
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2000507444	T2	20000620	JP 1997-534527	19970320
	US 6165793	A	20001226	US 1998-75511	19980508
	US 6180406	B1	20010130	US 1998-99015	19980617
	AU 9923816	A1	19990812	AU 1999-23816	19990416
PRAI	US 1995-564955	19951130			
	US 1994-198431	19940217			
	AU 1995-29714	19950217			
	US 1995-425684	19950418			
	US 1996-537874	19960304			

US 1996-621430 19960325
US 1996-621859 19960325
US 1996-650400 19960520
EP 1996-940934 19961202
JP 1997-520744 19961202
WO 1996-US19256 19961202
WO 1997-US4715 19970320

AB A method for DNA reassembly after random fragmentation, and its application to mutagenesis of nucleic acid sequences by in vitro or in vivo recombination is described. In particular, a method for the prodn. of nucleic acid fragments or polynucleotides encoding mutant proteins is described. The present invention also relates to a method of repeated cycles of mutagenesis, **shuffling** and selection which allow for the directed mol. evolution in vitro or in vivo of proteins. Using these methods Aequoreas victorias green fluorescent protein was mutagenized to a form with a 45-fold improvement in fluorescence signal. The DNA **shuffling** method, when applied to arsenate detoxification bacteria, improved arsenate resistance 50-100-fold.

RE.CNT 201
RE
(1) Andersson; PNAS 1996, V93, P906 HCAPLUS
(2) Anon; EP 552266 HCAPLUS
(3) Anon; EP 252666 B1 1988 HCAPLUS
(4) Anon; WO 9007576 1990 HCAPLUS
(5) Anon; WO 9014430 1990 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 9 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:628261 HCAPLUS
DN 133:218482
TI Generation of sequence variants by recombination, post-transcriptional processing or intein processing
IN **Patten, Phillip A.**; Heinrichs, Volker; **Stemmer, Willem P. C.**
PA Maxygen, Inc., USA
SO PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000052155	A2	20000908	WO 2000-US5573	20000303

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-122943 19990305
US 1999-142299 19990702
US 1999-164617 19991110
US 1999-164618 19991110

AB Methods of modulating, tuning and improving hybridization properties and recombination properties of mols. for use in nucleic acid **shuffling** procedures, relates recombination mixts. and methods of modulating, tuning, improving and evolving splicing of RNAs and proteins are provided. Methods of generating sequence variants using recombination and recombination-like processes, such as RNA splicing at different levels of the process of gene expression are described. New sequences are generated using recombining insertion sequences, RNA splicing, or protein splicing.

L86 ANSWER 10 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:628259 HCAPLUS
DN 133:218481
TI Gene **shuffling** for rapid production of surrogate orphan ligands for orphan receptors
IN Howard, Russell J.; **Patten, Phillip A.**
PA Maxygen, Inc., USA
SO PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000052153	A2	20000908	WO 2000-US5764	20000301

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-122569 19990302
AB This invention provides methods for obtaining surrogate ligands for orphan receptors, as well as surrogate receptors for orphan ligands. The methods are also useful for obtaining optimized ligands and/or receptors that exhibit an enhanced ability to modulate a biol. activity compared to a naturally occurring cognate receptor or cognate ligand. The methods involve (1) creating a library of recombinant polynucleotides, and (2) screening the library to identify a recombinant polynucleotide that encodes a surrogate ligand that can specifically bind to a ligand binding domain of the orphan receptor and/or modulate the activity of the orphan receptor. The library of recombinant polypeptides is obtained by recombining at least first and second forms of a nucleic acid, each of which forms encodes a ligand for a member of a receptor family or a fragment of said ligand. The screening methods involve expressing the library of recombinant polynucleotides, and contacting the resulting library of candidate surrogate ligands with a test cell that contains a polypeptide which comprises: (a) a ligand binding domain of the orphan receptor (which can be an extracellular domain of the receptor); and (b) a cytoplasmic and/or DNA-binding domain of a second receptor. Thus, in vitro DNA **shuffling** was used to breed a family of over 20 human interferon-.alpha. genes for increased antiviral and anti-proliferation activity in murine cells. DNA **shuffling** was also exemplified with natural ligands for the CCR5 chemokine receptor.

L86 ANSWER 11 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:628253 HCAPLUS
DN 133:218480
TI Encryption of traits using split gene sequences, methods of unencrypting encrypted genes, and uses of the system
IN **Patten, Phillip A.**; Lassner, Michael; Yamamoto, Takashi; Carr, Brian; Ness, Jon E.; Bermudez, Ericka R.
PA Maxygen, Inc., USA
SO PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000052146	A2	20000908	WO 2000-US5448	20000303

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,

IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-122943 19990305
US 1999-142299 19990702
US 1999-164617 19991110
US 1999-164618 19991110

AB Methods of unencrypting trait-encrypted gene sequences to provide unencrypted RNAs or proteins is disclosed. The invention also relates to methods of encrypting traits including splitting genes between two parental organisms or between a host organism and a vector. The gene sequences are unencrypted when the two parental organisms are mated or when the vector infects the host organism by trans-splicing either the split RNAs or split proteins upon expression of the split gene sequences. The invention also includes methods of providing multiple levels of trait encryption and reliable methods of producing hybrid organisms. Addnl. methods include those related to unencrypting engineered genetic elements to provide protein functions and those directed at recombining non-overlapping gene sequences. The invention also includes integrated systems and various compns. related to the disclosed methods.

L86 ANSWER 12 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:597549 HCAPLUS
DN 133:276805
TI Directed evolution: the "**rational**" basis for "irrational" design
AU **Tobin, Matthew B.; Gustafsson, Claes**; Huisman, Gjalt W.
CS Maxygen Inc., Redwood City, CA, 94063, USA
SO Curr. Opin. Struct. Biol. (2000), 10(4), 421-427
CODEN: COSBEF; ISSN: 0959-440X
PB Elsevier Science Ltd.
DT Journal; General Review
LA English
AB A review, with 57 refs. The development of powerful genetic manipulation formats has revolutionized the creation of functional biol. mols. Recent advances in directed evolution demonstrate that multiple properties of proteins can be optimized simultaneously and rapidly. Improved proteins often contain multiple and dispersed substitutions that act synergistically to improve enzyme properties and function. The benefits of such multiple changes are often not predictable from a priori structural knowledge. Furthermore, alternative solns. to gaining functional change can be obtained.

RE.CNT 57
RE
(1) Altamirano, M; Nature 2000, V403, P617 HCAPLUS
(2) Arnold, F; Accounts Chem Res 1998, V31, P125 HCAPLUS
(3) Arnold, F; Ann NY Acad Sci 1999, V870, P400 HCAPLUS
(4) Arnold, F; Curr Opin Chem Biol 1999, V3, P54 HCAPLUS
(5) Bornscheuer, U; Agnew Chem Int Ed Engl 1998, V37, P3105 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 13 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:589937 HCAPLUS
DN 133:173041
TI Coenzyme A disulfide reductase, and inhibitors thereof as antimicrobial agents
IN Katz, Leonard; **Delcardayre, Stephen B.**; Davies, Julian E.
PA University of British Columbia, Can.
SO U.S., 48 pp.
CODEN: USXXAM
DT **Patent**
LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6107068	A	20000822	US 1997-886886	19970702
	WO 9723628	A1	19970703	WO 1996-US20017	19961219

W: CA, JP, MX, US
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRAI US 1995-9146 19951222
WO 1996-US20017 19961219

AB Isolated and purified CoA disulfide reductase (CoADR) enzymes are provided. The gene and protein sequences are provided for CoADR from Staphylococcus aureus, S. epidermidis, Enterococcus faecalis, and two isoforms from E. faecium. Oligonucleotides encoding the CoADR, vectors and host cells contg. such oligonucleotides are also provided. In addn., antibodies reactive with the CoADR are provided, as are methods of isolating the CoADR, producing recombinant CoADR, using CoADR for screening compds. for CoADR-modulating activity, and detecting organisms which produce CoADR a test sample. Methods for identifying a gene encoding a CoADR are also provided.

RE.CNT 16
RE
(1) Bellamacina; The FASEB Journal 1996, V10, P1257 HCAPLUS
(2) Carrico; US 5200313 1993 HCAPLUS
(3) Claiborne; Trends in Biochemical Sciences 1992, V17, P183 HCAPLUS
(4) Fahey; Advances in Enzymology and Related Areas of Molecular Biology 1991, P1 HCAPLUS
(5) Fahey; Journal of Bacteriology 1978, V133, P1126 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 14 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:583897 HCAPLUS
DN 134:25941
TI Molecular breeding of viruses
AU Soong, Nay-Wei; Nomura, Laurel; Pekrun, Katja; Reed, Margaret; Sheppard, Liana; Dawes, Glenn; **Stemmer, Willem P. C.**
CS Maxygen Inc., Redwood City, CA, USA
SO Nat. Genet. (2000), 25(4), 436-439
CODEN: NGENEC; ISSN: 1061-4036
PB Nature America Inc.
DT Journal
LA English
AB Genetic recombination is a major force driving the evolution of many viruses. Recombination between two copackaged retroviral genomes may occur at rates as high as 40% per replication cycle1. This enables genetic information to be **shuffled** rapidly, leading to recombinants with new patterns of mutations and phenotypes. The in vitro process of DNA **shuffling2**,3 (mol. breeding) mimics this mechanism on a vastly parallel and accelerated scale. Multiple homologous parental sequences are recombined in parallel, leading to a diverse library of complex recombinants from which desired improvements can be selected. Different proteins and enzymes have been improved using DNA **shuffling4**-6. We report here the first application of mol. breeding to viruses. A single round of **shuffling** envelope sequences from six murine leukemia viruses (MLV) followed by selection yielded a chimeric clone with a completely new tropism for Chinese Hamster Ovary (CHOK 1) cells. The compn. and properties of the selected clone indicated that this particular permutation of parental sequences cannot be readily attained by natural retroviral recombination. This example demonstrates that mol. breeding can enhance the inherently high evolutionary potential of retroviruses to obtain desired phenotypes. It can be an effective tool, when information is limited, to optimize viruses for gene therapy and vaccine applications when multiple complex functions must be simultaneously balanced.

RE.CNT 16
RE
(1) Chang, C; Nature Biotechnol 1999, V17, P793 HCAPLUS

(2) Coffin, J; Curr Top Microbiol Immunol 1992, V176, P143 HCAPLUS
(3) Colicelli, J; J Mol Biol 1988, V199, P47 HCAPLUS
(4) Crameri, A; Nature 1998, V391, P288 HCAPLUS
(5) Crameri, A; Nature Biotechnol 1996, V14, P315 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 15 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:490791 HCAPLUS
DN 133:116716
TI Ketosynthase domains of epothilone polyketide synthase from Sorangium cellulosum
IN **Gustafsson, Claes**; Betlach, Mary C.
PA Kosan Bioscience, USA
SO U.S., 39 pp.
CODEN: USXXAM
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6090601	A	20000718	US 1998-10809	19980123

AB Domains of epothilone polyketide synthase of Sorangium cellulosum SMP44, and polynucleotides encoding therefor are provided. Addnl., chimeric polyketide synthases that include domains, or subsets of domains, patterned on epothilone polyketide synthase. Methods to prep. epothilone in pharmaceutically useful quantities are described, as are methods to prep. polyketide combinatorial libraries.
RE.CNT 26
RE
(1) Aigle; Microbiology 1996, V142, P2815 HCAPLUS
(2) Anon; WO 9313663 1993 HCAPLUS
(3) Anon; WO 9508548 1995 HCAPLUS
(4) Anon; WO 9640968 1996 HCAPLUS
(5) Anon; EP 0791655 1997 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 16 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:444373 HCAPLUS
TI Molecular breeding by DNA **shuffling**
AU Punnonen, Juha; Whalen, Robert G.; **Patten, Phillip A.**; **Stemmer, Willem P. C.**
CS USA
SO Sci. Med. (Philadelphia) (2000), 7(2), 38-47
CODEN: SCMEFJ; ISSN: 1087-3309
PB Science & Medicine
DT Journal
LA English
AB DNA **shuffling** followed by screening, also called "mol. breeding," is a technol. that enables rapid directed evolution of genes in a process that mimics natural evolution. Focused selection pressure under lab. conditions allows DNA **shuffling** to generate improved variants in a short time and to select for desirable properties that would not possess a selective advantage in nature. The technol. has potential applications in vaccines, immunotherapeutics, protein pharmaceuticals, gene therapy, agriculture, and the chem. industry.

L86 ANSWER 17 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:335541 HCAPLUS
DN 132:344113
TI DNA sequence **shuffling** methods for producing plants and agricultural photosynthetic microbes with an improved ADP-glucose pyrophosphorylase phenotypes
IN **Stemmer, Willem P. C.**; Subramanian, Venkiteswaran
PA Maxygen, Inc., USA
SO PCT Int. Appl., 85 pp.
CODEN: PIXXD2

DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000028018	A1	20000518	WO 1999-US26797	19991109

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1998-107782 19981110
AB The invention provides methods for generating novel or improved ADP-glucose pyrophosphorylase (ADPGPP) genetic sequences, that, when transferred into appropriate plant cell, or photosynthetic microbial host and expressed therein, confers an enhanced metabolic phenotype to the host to increase starch formation ratio and/or rate, or to increase the accumulation or depletion of certain starches by using recursive genetic recombination. In an aspect, the invention provides a **shuffled** ADPGPP which is catalytically active and which exhibits an improved enzymic profile, such as an increased Km for inhibitor, decreased Km for activator, and or a decreased Km for substrate, increased Vmax, reduced pH sensitivity, or the like. This invention further relates to generating improved agronomically and horticulturally important starch prodn. plant and microorganism phenotypes which do not naturally occur or would be anticipated to occur at a substantial frequency in nature.
RE.CNT 8
RE
(1) Crameri, A; MACMILLAN JOURNALS LTD 1998, V391, P288 HCAPLUS
(2) Danisco; WO 9424292 A 1994 HCAPLUS
(3) Greene, T; PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA 1998, V95(17), P10322 HCAPLUS
(4) Harayama, S; TRENDS IN BIOTECHNOLOGY 1998, V16(2) HCAPLUS
(5) Novonordisk As; WO 9841622 A 1998 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 18 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:335540 HCAPLUS
DN 132:344112
TI DNA sequence **shuffling** methods for producing plants and agricultural photosynthetic microbes with improved phosphoenolpyruvate carboxylase phenotypes
IN **Stemmer, Willem P. C.**; Subramanian, Venkiteswaran
PA Maxygen, Inc., USA
SO PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000028017	A1	20000518	WO 1999-US26771	19991109

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1998-107757 19981110

AB The invention provides methods for generating novel or improved phosphoenolpyruvate carboxylase (PEPC) genetic sequences, that, when transferred into appropriate plant cell, or photosynthetic microbial host and expressed therein, confers an enhanced metabolic phenotype to the host to increase carbon fixation ratio and/or rate, or to increase the accumulation or depletion of certain metabolites and energy storage sinks by using recursive genetic recombination. In an aspect, the invention provides a **shuffled** PEPC which is catalytically active and which exhibits an improved enzymic profile, such as an increased Km for inhibitor, decreased Km for activator, and or a decreased Km for substrate, increased Vmax, reduced pH sensitivity, or the like. This invention further relates to generating improved agronomically and horticulturally important starch prodn. plant and microorganism phenotypes which do not naturally occur or would be anticipated to occur at a substantial frequency in nature.

RE.CNT 6

RE

(1) Chollet, R; ANNUAL REVIEW OF PLANT PHYSIOLOGY AND PLANT MOLECULAR BIOLOGY 1996, V47, P273 HCAPLUS

(2) Crameri, A; MACMILLAN JOURNALS LTD 1998, V391, P288 HCAPLUS

(3) Harayama, S; TRENDS IN BIOTECHNOLOGY 1998, V16(2) HCAPLUS

(4) Morikawa, M; JOURNAL OF BIOCHEMISTRY 1977, V81(5), P1473 HCAPLUS

(5) Novonordisk As; WO 9841622 A 1998 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 19 OF 86 HCAPLUS COPYRIGHT 2001 ACS

AN 2000:335531 HCAPLUS

DN 132:344089

TI Production of modified ribulose 1,5-bisphosphate carboxylase/oxygenase with improved properties by nucleic acid **shuffling** and selection

IN **Stemmer, Willem P. C.**; Subramanian, Venkitswaran; Zhu, Genhai; Liu, Li; **Selifonov, Sergey A.**

PA Maxygen, Inc., USA

SO PCT Int. Appl., 104 pp.
CODEN: PIXXD2

DT **Patent**

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000028008	A1	20000518	WO 1999-US26772	19991109

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1998-107756 19981110

US 1999-153093 19990909

AB The invention relates to methods and compns. for generating, modifying, adapting, and optimizing polynucleotide sequences that encode proteins having Rubisco biosynthetic enzyme activities which are useful for introduction into plant species, agronomically-important microorganisms, and other hosts, and related aspects. In general, polynucleotide sequence **shuffling** and phenotype selection, such as detection of a parameter of Rubisco enzyme activity, is employed recursively to generate polynucleotide sequences which encode novel proteins having desirable Rubisco enzymic catalytic function(s), regulatory function(s), and related enzymic and physicochem. properties. The method is applied to both regulatory subunit (small subunit, gene rbcS) and catalytic subunit (large subunit, gene rbcL), resp., as appropriate for Form I and Form II Rubisco. Selection from a **shuffled** nucleic acid library is achieved such that the Km for CO2 or O2, or the carbon fixation activity, is

significantly changed from naturally occurring Rubisco.

RE.CNT 7

RE

(1) Crameri, A; NATURE 1998, V391, P288 HCAPLUS
(2) Flachmann, R; PLANT PHYSIOLOGY 1997, V114(1), P131 HCAPLUS
(3) Jamet, E; JOURNAL OF MOLECULAR EVOLUTION 1991, V33(3) HCAPLUS
(5) Maxygen Inc; WO 9735966 A 1997 HCAPLUS
(7) Wolter, F; PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA 1988, V85, P846 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 20 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:327310 HCAPLUS
TI Generating new biocatalysts by molecular breeding.
AU **delCardayre, Stephen B.**; Zhang, Ying-Xin; Huisman, Gjalt W.
CS Maxygen, Inc, Redwood City, CA, 94063, USA
SO Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000 (2000), BIOT-088 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69CLAC
DT Conference; Meeting Abstract
LA English
AB Mol. Breeding is a method of directed evolution that is extremely robust for manipulating biomol. function. Mol. Breeding has been applied to improve heterologous protein expression and function, to alter enzyme specificity, to adapt enzyme activity to different environments, and to improve metabolic pathways and fermn. processes. A primary goal of metabolic engineering is the alteration of a cell to improve its ability to efficiently catalyze a specific set of chem. transformations. Achieving this goal often requires heterologous genes to be functionally expressed, layers of pathway regulation to be relaxed, feedstocks to be funneled through specific metabolic pathways, and for this to occur under conditions (the fermenter) alien to a cells natural environment. Similar to the rational design of polypetides, "cut and paste" approaches to metabolic engineering must rely on assumptions that discount the complexity of biol. systems. Gene, pathway, and genome **shuffling** employ mechanisms of natural biol. evolution and provide empirical complements to metabolic engineering that accelerate the generation of new biocatalysts. Results of these approaches shall be discussed.

L86 ANSWER 21 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:326564 HCAPLUS
TI Molecular breeding of genes, pathways, and genomes by DNA **shuffling**.
AU **Stemmer, Willem P. C.**
CS Maxygen, Inc, Redwood City, CA, 94063, USA
SO Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000 (2000), AGFD-104 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69CLAC
DT Conference; Meeting Abstract
LA English
AB We have developed mol. breeding formats for single genes, pathways, episomes, viruses and whole microbial genomes. Our goal is to mimic the process of classical breeding. An important advantage of this approach is that it does not require much information. DNA **shuffling** is a reliable method for homologous recombination of pools of related sequences. Libraries of chimeras are constructed from homologous DNA sequences obtained from natural diversity. The pool of the best clones obtained after one cycle of screening is re-**shuffled** to create the next library of chimeras. Screening of these libraries using a variety of high throughput anal. techniques identifies pos. combinations of sequences while removing neg. combinations of sequences. The application of this process to a broad range of specific examples will be described.

L86 ANSWER 22 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:227769 HCAPLUS
DN 132:261360
TI **Shuffling** of codon-altered genes for forced evolution of protein or nucleic acid products
IN **Patten, Phillip A.**; Liu, Lu; **Stemmer, Willem P. C.**
PA Maxygen, Inc., USA
SO PCT Int. Appl., 92 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000018906	A2	20000406	WO 1999-US22588	19990928
WO 2000018906	A3	20001026		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

WO 2000042561	A3	20001207	WO 2000-US1203	20000118

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1998-102362 19980929
US 1999-117729 19990129
US 1999-118813 19990205
US 1999-141049 19990624
US 1999-116447 19990119
US 1999-118854 19990205
US 1999-408392 19990928
US 1999-408393 19990928
US 1999-416375 19991012
US 1999-416837 19991012

AB The present invention provides methods of accessing a completely different mutational spectrum for a selected protein than is available in the naturally occurring nucleic acid encoding the protein. This increases the type and rate of forced evolution for the selected protein, allowing for rapid improvement of any detectable characteristic of the protein. In the methods, nucleic acids are synthesized with altered codon usage, and/or which encode one or several amino acid residue changes as compared to the selected protein, where the amino acid and codon usage changes can be conservative or non-conservative. The resulting codon/amino acid modified nucleic acid(s) are recombined using DNA **shuffling** techniques with either the native nucleic acid, or with each other (or both), typically using recursive **shuffling** methods. The nucleic acids or the encoded protein are than screened for a desirable property.

L86 ANSWER 23 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:161424 HCAPLUS
DN 132:191901
TI Transformation, selection, and screening of sequence-**shuffled** polynucleotides for development and optimization of plant phenotypes
IN **Stemmer, Willem P. C.**; Subramanian, Venkiteswaran
PA Maxygen, Inc., USA

SO PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000012680	A1	20000309	WO 1999-US19732	19990830

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9956968	A1	20000321	AU 1999-56968	19990830
PRAI US 1998-98528	19980831			
WO 1999-US19732	19990830			

AB The invention relates to methods and compns. for generating, modifying, adapting, and optimizing polynucleotide sequences that confer detectable phenotypic properties on plant species, and related aspects. The method involves transforming populations of plant protoplasts with a library of **shuffled** sequences e.g. an array of randomly mutagenized sequences, screening and selecting transformants. Transformant are evaluated and may be transformed again with a new array of DNA fragments. The method is described using development of glyphosate-resistant EPSP synthases as an example. The method used EPSP synthase genes from a no. of plants (Arabidopsis, tomato, tobacco, maize etc.). The genes are **shuffled** by random cleavage with DNase I followed by size selection and reassembly by religation. Tobacco protoplasts are transformed with the resulting library and screened for glyphosate resistance.

RE.CNT 2
RE
(1) Bayley; Plant Molecular Biology 1992, V18, P353 HCAPLUS
(2) Lyznik; Nucl Acids Res 1993, V21(4), P969 HCAPLUS

L86 ANSWER 24 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:133865 HCAPLUS
DN 132:190496
TI DNA **shuffling** to produce herbicide-selective crops
IN Subramanian, Venkitswaran; **Stemmer, Willem P. C.**; Castle, Linda A.; Muchhal, Umesh S.; Siehl, Daniel L.
PA Maxygen Inc., USA
SO PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000009727	A2	20000224	WO 1999-US18394	19990812
WO 2000009727	A3	20000518		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9954822	A1	20000306	AU 1999-54822	19990812
PRAI US 1998-96288	19980812			

US 1998-111146 19981207
US 1998-112746 19981217
WO 1999-US18394 19990812

AB Methods of **shuffling** DNA to obtain recombinant herbicide tolerance nucleic acids encoding proteins having new or improved herbicide tolerance activities, libraries of **shuffled** herbicide tolerance nucleic acids, transgenic plants, and DNA **shuffling** mixts. are provided. Thus, a parental nucleic acid encoding a herbicide-metabolizing enzyme is obtained and a library of variant forms obtained by DNA **shuffling** recombination; the library is screened to identify at least one recombinant herbicide tolerance nucleic acid. The method is exemplified by **shuffling** of Arabidopsis or tomato 5-enolpyruvoylshikimate 3-phosphate synthase cDNA for glyphosate tolerance in plant AB2829 cells.

L86 ANSWER 25 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:133824 HCAPLUS
DN 132:162018
TI DNA **shuffling** of monooxygenase genes for production of industrial chemicals
IN Affholter, Joseph A.; Davis, Christopher; **Selifonov, Sergey A.**
PA Maxygen, Inc., USA
SO PCT Int. Appl., 153 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000009682	A1	20000224	WO 1999-US18424	19990812
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9953479	A1	20000306	AU 1999-53479	19990812

PRAI US 1998-96271 19980812
US 1999-130810 19990423
WO 1999-US18424 19990812
OS MARPAT 132:162018

AB This invention provides improved monooxygenases, dehydrogenases, and transferases that are useful for the biocatalytic synthesis of compds. such as .alpha.-hydroxycarboxylic acids, and aryl- and alkyl-, hydroxy compds. The polypeptides provided herein are improved in properties such as regioselectivity, enzymic activity, stereospecificity, and the like. Methods for obtaining recombinant polynucleotides that encode these improved polypeptides are also provided, as are organisms that express the polypeptides and are thus useful for carrying out said biocatalytic syntheses. In the methods for obtaining monooxygenase genes, a plurality of parental forms (homologs) of a selected nucleic acid are recombined. The selected nucleic acid derived either from one or more parental nucleic acid(s) which encodes a monooxygenase enzyme, or a fragment thereof, or from a parental nucleic acid which does not encode monooxygenase, but which is a candidate for DNA **shuffling** to develop monooxygenase activity. The plurality of forms of the selected nucleic acid differ from each other in at lease one (and typically two or more) nucleotides, and, upon recombination, provide a library of recombinant monooxygenase nucleic acids. The library can be an in vitro set of mols., or present in cells, phage or the like. The library is screened to identity at least one recombinant monooxygenase nucleic acid that exhibits distinct or improved monooxygenase activity compared to the parental nucleic acid or nucleic acids. Also provided by the invention are methods for increasing said

solvent resistance of organisms that are used in the synthetic methods.
RE.CNT 18
RE
(1) Affymax Tech Nv; WO 9720078 A 1997 HCAPLUS
(2) Agency Of Ind Sci & Technology; JP 05-049474 A 1993 HCAPLUS
(3) Aoyama, T; JOURNAL OF BIOLOGICAL CHEMISTRY 1989, V264(18), P10388 HCAPLUS
(4) Crameri, A; NATURE 1998, V391, P288 HCAPLUS
(5) Dierks, E; THE JOURNAL OF BIOLOGICAL CHEMISTRY 1998, V273(36), P23055 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 26 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:68598 HCAPLUS
DN 132:103762
TI Evolution of whole cells and organisms by recursive sequence recombination
IN **Del Cardayre, Stephen; Tobin, Matthew; Stemmer, Willem P. C.**; Ness, Jon E.; **Minshull, Jeremy; Patten, Phillip A.**; Subramanian, Venkiteswatan; Castle, Linda A.; Krebber, Claus M.; Bass, Steve; Zhang, Ying-Xin; Cox, Tony; Huisman, Gjalt; Yuan, Ling; Affholter, Joseph A.
PA Maxygen, Inc., USA
SO PCT Int. Appl., 197 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000004190	A1	20000127	WO 1999-US15972	19990715
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9951026	A1	20000207	AU 1999-51026	19990715

PRAI US 1998-116188 19980715
WO 1999-US15972 19990715
AB The invention provides methods employing iterative cycles of recombination and selection and screening for evolution of whole cells and organisms toward acquisition of desired properties. The method involves transforming target cells or organisms with a DNA library, e.g. an array of randomly mutagenized sequences, screening and selecting transformants. Transformant are evaluated and may be transformed again with a new array of DNA fragments. Methods of generating and selecting heteroduplex DNA for mutagenic transformation are also described. Examples of such properties include enhanced recombinogenicity, genome copy no., and capacity for expression and/or secretion of proteins and secondary metabolites.
RE.CNT 10
RE
(1) Carlson; US 5837470 A 1998 HCAPLUS
(2) Ferenczy; US 4729951 A 1988 HCAPLUS
(5) Julien; US 5869718 A 1999 HCAPLUS
(6) Sherwin; US 5578461 A 1996 HCAPLUS
(7) Thompson; US 5824485 A 1998 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 27 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:20726 HCAPLUS
DN 132:177374
TI Improving the Catalytic Activity of a Thermophilic Enzyme at Low Temperatures

AU Merz, Astrid; Yee, Muh-ching; Szadkowski, Halina; Pappenberger, Guenter; Crameri, Andreas; **Stemmer, Willem P. C.**; Yanofsky, Charles; Kirschner, Kasper
CS Department of Biophysical Chemistry, Biozentrum, Basel, 4056, Switz.
SO Biochemistry (2000), 39(5), 880-889
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
AB Enzymes from thermophilic organisms often are barely active at low temps. To obtain a better understanding of this sluggishness, we used DNA **shuffling** to mutagenize the trpC gene, which encodes indoleglycerol phosphate synthase, from the hyperthermophile Sulfolobus solfataricus. Mutants producing more active protein variants were selected by genetic complementation of an Escherichia coli mutant bearing a trpC deletion. Single amino acid changes and combinations of these changes improved growth appreciably. Five singly and doubly altered protein variants with changes at the N- and C-termini, or at the phosphate binding site, were purified and characterized with regard to their kinetics of enzymic catalysis, product binding, cleavage by trypsin, and inactivation by heat. Turnover nos. of the purified variant proteins correlated with the corresponding growth rates, showing that the turnover no. was the selected trait. Although the affinities for both the substrate and the product decreased appreciably in most protein variants, these defects were offset by the accumulation of high levels of the enzyme's substrate. Rapid mixing of the product indoleglycerol phosphate with the parental enzyme revealed that the enzyme's turnover no. at low temps. is limited by the dissocn. of the enzyme-product complex. In contrast, representative protein variants bind and release the product far more rapidly, shifting the bottleneck to the preceding chem. step. The turnover no. of the parental enzyme increases with temp., suggesting that its structural rigidity is responsible for its poor catalytic activity at low temps. In support of this interpretation, the rate of trypsinolysis or of thermal denaturation is accelerated significantly in the activated protein variants.
RE.CNT 39
RE
(1) Aguilar, C; J Mol Biol 1997, V271, P789 HCAPLUS
(4) Creighton, T; J Biol Chem 1968, V243, P5605 HCAPLUS
(5) Creighton, T; Methods Enzymol 1970, V17, P365 HCAPLUS
(6) Darimont, B; Protein Sci 1998, V7, P1221 HCAPLUS
(9) Eberhard, M; Biochemistry 1995, V34, P5419 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 28 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:723045 HCAPLUS
DN 131:333002
TI Optimization of plant pest resistance genes using DNA **shuffling**
IN **Stemmer, Willem P. C.**; Castle, Linda; Yamamoto, Takashi
PA Maxygen, Inc., USA
SO PCT Int. Appl., 99 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9957128	A1	19991111	WO 1999-US8473	19990422

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,

CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
AU 9936508 A1 19991123 AU 1999-36508 19990422
EP 1073670 A1 20010207 EP 1999-918645 19990422
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
PRAI US 1998-122054 19980501
US 1998-94462 19980728
WO 1999-US8473 19990422

AB This invention provides methods of obtaining pest resistance genes that are improved over naturally occurring genes for use in conferring upon plants resistance to pests. The methods involve (1) the use of DNA **shuffling** of pest resistance genes to produce libraries of recombinant pest resistance genes, which are then (2) screened to identify those that exhibit the improved property or properties of interest. In some embodiments, the methods also involve (3) recombining at least one optimized recombinant pest resistance gene with a further form of the pest resistance gene, which is the same or different from one or more of the plurality of nucleic acid forms of (1), to produce a further library of recombinant pest resistance genes; (4) screening the further library to identify at least one further optimized recombinant pest resistance gene that exhibits a further improvement in pest resistance capability compared to a non-recombinant pest resistance gene. The method repeats (3) and (4) as necessary until the further optimized recombinant vector module exhibits a further improvement in pest resistance capability compared to a no-recombinant pest resistance gene. The invention also provides libraries that contain a plurality of recombinant pest resistance genes, where each recombinant pest resistance gene contains different permutations of segments of a gene which can confer upon a plant resistance to the plant. The method is exemplified by **shuffling** of insecticidal toxin genes (cry18Aa and cry2) of Bacillus popilliae or B. thuringiensis to yield toxins with improved activity against corn rootworm or other nematodes.

RE.CNT 4
RE
(1) Driver; US 5640804 A 1997 HCAPLUS
(2) Koch; US 5882851 A 1999 HCAPLUS
(3) Thompson; US 5874288 A 1999 HCAPLUS
(4) Van Rie; US 5659123 A 1997 HCAPLUS

L86 ANSWER 29 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:612198 HCAPLUS
DN 131:309678
TI Evolution of a cytokine using DNA family **shuffling**
AU Chang, Chia-Chun J.; Chen, Teddy T.; Cox, Brett W.; Dawes, Glenn N.; **Stemmer, Willem P. C.**; Punnonen, Juha; **Patten, Phillip A.**
CS Maxygen, Inc., Santa Clara, CA, 95051, USA
SO Nat. Biotechnol. (1999), 17(8), 793-797
CODEN: NABIF9; ISSN: 1087-0156
PB Nature America
DT Journal
LA English

AB DNA **shuffling** of a family of over 20 human interferon-.alpha. (Hu-IFN-.alpha.) genes was used to derive variants with increased antiviral and antiproliferation activities in murine cells. A clone with 135,000-fold improved specific activity over Hu-IFN-.alpha.2a was obtained in the first cycle of **shuffling**. After a second cycle of selective **shuffling**, the most active clone was improved 285,000-fold relative to Hu-IFN-.alpha.2a and 185-fold relative to Hu-IFN-.alpha.1. Remarkably, the three most active clones were more active than the native murine IFN-.alpha.s. These chimeras are derived from up to five parental genes but contained no random point mutations. These results demonstrate that diverse cytokine gene families can be used as starting material to rapidly evolve cytokines that are more active, or have superior selectivity profiles, than native cytokine genes.

RE.CNT 32
RE

(2) Blatt, L; J Interferon Cytokine Res 1996, V16, P489 HCAPLUS
(5) Dusheiko, G; Hepatology 1997, V26, P112S HCAPLUS
(6) Fish, E; J Interferon Res 1992, V12, P257 HCAPLUS
(7) Fuh, G; Science 1992, V256, P1677 HCAPLUS
(11) Henco, K; J Mol Biol 1985, V185, P227 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 30 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:577380 HCAPLUS
TI DNA **shuffling** of subgenomic sequences of subtilisin
AU Ness, Jon E.; Welch, Mark; **Giver, Lori**; Bueno, Manuel; Cherry, Joel R.; Borchert, Torben V.; **Stemmer, Willem P. C.**; **Minshull, Jeremy**
CS Maxygen, Santa Clara, CA, 95051, USA
SO Nat. Biotechnol. (1999), 17(9), 893-896
CODEN: NABIF9; ISSN: 1087-0156
PB Nature America
DT Journal
LA English
AB DNA family **shuffling** of 26 protease genes was used to create a library of chimeric proteases that was screened for four distinct enzymic properties. Multiple clones were identified that were significantly improved over any of the parental enzymes for each individual property. Family **shuffling**, also known as mol. breeding, efficiently created all of the combinations of parental properties, producing a great diversity of property combinations in the progeny enzymes. Thus, mol. breeding, like classical breeding, is a powerful tool for recombining existing diversity to tailor biol. systems for multiple functional parameters.
RE.CNT 33
RE
(1) Beebe, A; Immunity 1997, V6, P551 HCAPLUS
(2) Bott, R; Enzyme engineering XI 1992, V672 HCAPLUS
(4) Bryan, P; Proteins 1986, V1, P326 HCAPLUS
(5) Carter, P; Proteins 1989, V6, P240 HCAPLUS
(6) Crameri, A; Nature 1998, V391, P288 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 31 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:561566 HCAPLUS
DN 131:181656
TI Thermally stable para-nitrobenzyl esterases
IN Arnold, Frances H.; **Giver, Lorraine J.**
PA California Institute of Technology, USA
SO U.S., 112 pp.
CODEN: USXXAM
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5945325	A	19990831	US 1998-62890	19980420

AB Specific modified para-nitrobenzyl esterases are disclosed which have improved thermal stability relative to the thermal stability of unmodified naturally occurring para-nitrobenzyl esterase. A method for isolating and identifying modified para-nitrobenzyl esterases which exhibit improved thermal stability relative to naturally occurring para-nitrobenzyl esterase is described. The method involves prepg. a library of modified para-nitrobenzyl esterase genes which have nucleotide sequences that differ from the nucleic acid segment which encodes for naturally occurring para-nitrobenzyl esterase. The library of modified para-nitrobenzyl genes is expressed to provide a plurality of modified enzymes. The clones expressing modified enzymes are then screened to identify which enzymes retain esterase activity after heat treatment at elevated temp. Thus, the aryl esterase gene of Bacillus subtilis was subjected to error-prone PCR to produce genes encoding enzymes with improved thermal stability and

specific activity. Mutant 6sF9 displayed a Tm of 66.degree. and specific activity of 0.16 relative to the wild-type enzyme values of 52.degree. and 0.05, resp.

RE.CNT 8

RE

(1) Arnold; US 5316935 1994 HCAPLUS
(2) Arnold; US 5741691 1998 HCAPLUS
(3) Arnold, F; Advances Biochem Engineering/Biotechnol 1997, V58, P1 HCAPLUS
(4) Arnold, F; The FASEB Journal 1993, V7, P744 HCAPLUS
(5) Cantwell; US 5468632 1995 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 32 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:529282 HCAPLUS
DN 131:154480
TI Methods for obtaining a cell-specific binding molecule that increases uptake and/or specificity of a genetic vaccine to a target cell
IN Punnonen, Juha; **Stemmer, Willem P. C.**; Howard, Russell; **Patten, Phillip A.**
PA Maxygen, Inc., USA
SO PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9941402	A2	19990819	WO 1999-US3023	19990210
	WO 9941402	A3	19991111		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9926742	A1	19990830	AU 1999-26742	19990210
	EP 1053343	A2	20001122	EP 1999-906949	19990210
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI US 1998-21769 19980211
US 1998-74294 19980211
WO 1999-US3023 19990210

AB The present invention provides methods for obtaining a cell-specific binding mol. that is useful for increasing uptake or specificity of a genetic vaccine to a target cell. The methods involve (1) creating a library of recombinant polynucleotides encoding polypeptides with a nucleic acid binding domain and polypeptides with a cell-specific binding domain; and (2) screening said library for recombinant polynucleotides that encode mols. that can bind to a nucleic acid and also to a cell-specific receptor. Specifically, the invention describes the use of the DNA **shuffling** method to evolve receptor binding components of enterotoxins derived from Vibrio cholerae and enterotoxigenic strains of E. coli for improved attachment to cell surface receptors and for improved entry to and transport across the cells of the intestinal epithelium. An antigen of interest can be fused to these toxin subunits to facilitate the screening of evolved enterotoxin subunits, and also to facilitate oral delivery of proteins. The invention also provides methods of evolving a bacteriophage-derived vaccine delivery vehicle to obtain a delivery vehicle having enhanced ability to enter a target cell.

L86 ANSWER 33 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:529264 HCAPLUS
DN 131:169280
TI Antigen library immunization

IN Punnonen, Juha; Bass, Steven H.; Whalen, Robert Gerald; Howard, Russell; **Stemmer, Willem P. C.**
PA Maxygen, Inc., USA
SO PCT Int. Appl., 153 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9941383	A1	19990819	WO 1999-US2944	19990210
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9932891	A1	19990830	AU 1999-32891	19990210
	EP 1054973	A1	20001129	EP 1999-932510	19990210
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI US 1998-21769 19980211
US 1998-74294 19980211
US 1998-105509 19981023
WO 1999-US2944 19990210

AB This invention is directed to antigen library immunization, which provides methods for obtaining recombinant multivalent antigens having improved properties for therapeutic and other uses. The methods are useful for obtaining improved antigens that can induce an immune response against pathogens, cancer, and other conditions, as well as antigens that are effective in modulating allergy, inflammatory and autoimmune diseases.

RE.CNT 3
RE
(1) Affymax Technologies N V; WO 9720078 A 1997 HCAPLUS
(2) Crameri, A; Nature 1998, V391(6664), P288 HCAPLUS
(3) Gritz, L; US 5691170 A 1997 HCAPLUS

L86 ANSWER 34 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:529250 HCAPLUS
DN 131:140500
TI Genetic vaccine vector engineering by DNA **shuffling**
IN Punnonen, Juha; **Stemmer, Willem P. C.**; Whalen, Robert Gerald; Howard, Russell
PA Maxygen, Inc., USA
SO PCT Int. Appl., 138 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9941369	A2	19990819	WO 1999-US3022	19990210
	WO 9941369	A3	19990923		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9932910	A1	19990830	AU 1999-32910	19990210
	EP 1056842	A2	20001206	EP 1999-932508	19990210
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, FI
PRAI US 1998-21769 19980211
US 1998-74294 19980211
WO 1999-US3022 19990210
AB This invention provides methods of obtaining vaccines by use of DNA **shuffling**. Through use of the claimed methods, vectors can be obtained which exhibit increased efficacy for use as genetic vaccines. Two or more genetic components are provided that confer upon the vaccine the ability to direct an immune response so as to achieve an optimal response to vaccination. For example, the genetic vaccines can include a component that provides optimal antigen release, a component that provides optimal prodn. of cytotoxic T lymphocytes, a component that directs release of an immunomodulator, a component that directs release of a chemokine, and/or a component that facilitates binding to, or entry into, a desired target cell type. For example, a component can confer improved binding to, and uptake of, the genetic vaccine to target cells such as antigen-expressing cells or antigen-presenting cells. Addnl. components include those that direct antigen peptides derived from uptake of an antigen into a cell to presentation on either Class I or Class II mols. For example, one can include a component that directs antigen peptides to presentation on Class I mols. and comprises a polynucleotide that encodes a protein such as tapasin, TAP-1 and TAP-2, and /or a component that directs antigen peptides to presentation on Class II mols. and comprises a polynucleotide that encodes a protein such as an endosomal or lysosomal protease.

L86 ANSWER 35 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:529249 HCAPLUS
DN 131:169279
TI Optimization of immunomodulatory properties of genetic vaccines
IN Punnonen, Juha; **Stemmer, Willem P. C.**; Whalen, Robert Gerald; Howard, Russell
PA Maxygen, Inc., USA
SO PCT Int. Appl., 105 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 4

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9941368	A2	19990819	WO 1999-US3020	19990210
WO 9941368	A3	19991216		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9926741	A1	19990830	AU 1999-26741	19990210
EP 1053312	A2	20001122	EP 1999-906948	19990210

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRAI US 1998-21769 19980211
US 1998-74294 19980211
WO 1999-US3020 19990210
AB This invention provides methods for obtaining mols. that can modulate an immune response, and immunomodulatory mols. obtained using the methods. The mols. find use, for example, in the tailoring of an immune response induced by a genetic vaccine for a desired purpose. The genetic vaccine vector may comprises cellular receptor (e.g. macrophage scavenger receptor, cytokine receptor or chemokine receptor), antigen (e.g. HBsAg), cytokine (e.g. interleukins and interferons), or costimulator (e.g. B7-1 or B7-2).

L86 ANSWER 36 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:468019 HCAPLUS
DN 131:112368
TI Nucleic acid amplification using oligonucleotide primers with partially complementary ends
IN **Stemmer, Willem P. C.**; Lipshutz, Robert J.
PA Glaxo Group Ltd., UK; Affymetrix, Inc.
SO U.S., 61 pp.
CODEN: USXXAM
DT **Patent**
LA English
FAN.CNT 8

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5928905	A	19990727	US 1996-675502	19960703
US 5834252	A	19981110	US 1995-425684	19950418
WO 9633207	A1	19961024	WO 1996-US5480	19960418
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
AU 9923816	A1	19990812	AU 1999-23816	19990416
PRAI US 1995-425684	19950418			
WO 1996-US5480	19960418			
AU 1995-29714	19950217			

AB Processes for amplifying and detecting a target nucleic acid sequence and for assembling large polynucleotides from component polynucleotides, each involving generating concatemers formed by PCR amplification of overlapping fragments using partially complementary primers, are described. The method can form concatemers of the target sequence without the need to go through denaturation cycles either using a rolling circle replication-like mechanism or as a result of linear hybridization of single stranded ends of amplification products. By combining a no. of long, partially overlapping single-stranded DNA fragments very large sequences can be assembled. When individual sequences are presented with some base heterogeneity, multiple alleles of the target sequence can be generated in a single test tube.
RE.CNT 20
RE
(1) Anon; WO 9605296 1996 HCAPLUS
(2) Cauthers; US 4458066 1984 HCAPLUS
(3) Grosz; US 5340728 1994 HCAPLUS
(4) Gyllensten; US 5066584 1991 HCAPLUS
(5) Horton; Gene 1989, V77, P61 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 37 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:392618 HCAPLUS
DN 131:54752
TI Multiple drug resistance (MDR) gene of Aspergillus fumigatus and use for screening of MDR inhibitors
IN Peery, Robert Brown; Skatrud, Paul Luther; **Tobin, Matthew Barry**
PA Eli Lilly and Company, USA
SO U.S., 25 pp.
CODEN: USXXAM
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5914246	A	19990622	US 1996-612734	19960308

AB The invention provides isolated nucleic acid compds. encoding a multiple drug resistance protein of Aspergillus fumigatus. Vectors and transformed host cells comprising the multiple drug resistance-encoding DNA of

Aspergillus fumigatus AfuMDR1 are also provided. The invention further provides assays which utilize these transformed host cells for screening of MDR inhibitors. The transformed fungal cell culture is grown in the presence of (i) an antifungal agent to which the untransformed fungal cell is sensitive, but to which the transformed host cell is resistant, and (ii) a compd. that is suspected of being an MDR inhibitor.

RE.CNT 19
RE
(2) Balzi, E; Biochimica et Biophysica Acta 1994, V1187, P152 HCAPLUS
(3) Balzi, E; Journal of Bioenergetics and Biomembranes 1995, V27(1), P71 HCAPLUS
(4) Ben-Yaacov, R; Antimicrobial Agents and Chemotherapy 1994, V38(4), P648 HCAPLUS
(6) Deeley; US 5489519 1996 HCAPLUS
(7) Gottesman, M; Annu Rev Biochem 1993, V62, P385 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 38 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:380398 HCAPLUS
DN 131:165772
TI Protein evolution by molecular breeding
AU **Minshull, Jeremy; Stemmer, Willem P. C.**
CS Maxygen Incorporated, Redwood City, CA, 94063, USA
SO Curr. Opin. Chem. Biol. (1999), 3(3), 284-290
CODEN: COCBF4; ISSN: 1367-5931
PB Current Biology Publications
DT Journal; General Review
LA English
AB A review with 42 refs. Natural evolution has guided the development of "mol. breeding" processes used in the lab. for the rapid modification of subgenomic sequences including single genes. The most significant recent development has been the in vitro permutation of natural diversity. Homologous recombination of multiple related sequences produced high-quality libraries of chimeric sequences encoding proteins with functions that differ dramatically from any of the parents. Increasingly powerful screening methods are also being developed, allowing these libraries to be screened for novel biocatalysts.

RE.CNT 42
RE
(1) Akanuma, S; Protein Sci 1998, V7, P698 HCAPLUS
(2) Bornscheuer, U; Biotechnol Bioeng 1998, V58, P554 HCAPLUS
(4) Buchholz, F; Nat Biotechnol 1998, V16, P657 HCAPLUS
(5) Christians, F; Nat Biotechnol 1999, V17, P259 HCAPLUS
(6) Crameri, A; Nature 1998, V391, P288 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 39 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:311214 HCAPLUS
DN 130:333708
TI Modification of virus tropism and host range by viral genome **shuffling**
IN **Stemmer, Willem P. C.**; Phillip, Patten; Soong, Nay Wei
PA Maxygen, Incorporated, USA
SO PCT Int. Appl., 113 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9923107	A1	19990514	WO 1998-US23107	19981030

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9914494 A1 19990524 AU 1999-14494 19981030

EP 1030861 A1 20000830 EP 1998-958450 19981030

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRAI US 1997-962236 19971031

WO 1998-US23107 19981030

AB The invention relates to a viral genome **shuffling** method and compns. for modifying a phenotype of a virus, such as viral tropism and host range, by iterative sequence recombination of variant viruses and selection of improved variants. The method comprises (1) contacting a cell strain, cell line, or non-human animal which does not naturally support substantial replication of a predetd. virus with at least one initial infectious virion or replicable genome of said predetd. virus under replication conditions, (2) recovering a plurality of replicated genome copies of said predetd. virus, either as virions or as viral genomes in polynucleotide form, wherein some or all of the replicated genome copies comprise a mutation relative to the initial infectious virion or replicable genome, (3) recombining a plurality of said replicated genome copies so as to **shuffle** the mutations, thereby generating a collection of recombined replicated genome copies, and (4) selecting or screening said collection of recombined replicated genome copies to obtain one or more replicable viral genome encoding at least one modified viral tropic phenotype. Thus, DNA **shuffling** was used to evolve a new tropism in ecotropic murine leukemia virus. A library of **shuffled** ecotropic envelopes cloned into full-length proviral genomes was selected for the ability to infect CHO-K1 cells. A dominant clone rapidly emerged during selection contg. an envelope that was a clear recombinant among three of the parental sequences. This recombinant envelope conferred infectivity for CHO-K1 cells through a novel mechanism.

RE.CNT 11

RE

(1) Conley, A; J Virol 1994, V68(11), P6994 HCAPLUS

(2) Forte, P; Immunogen 1993, V38, P455 HCAPLUS

(3) Harouse, J; J Virol 1996, V70(10), P7290 HCAPLUS

(4) He, J; Nature 1997, V385, P645 HCAPLUS

(5) Joag, S; J Virol 1996, V70(5), P3189 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 40 OF 86 HCAPLUS COPYRIGHT 2001 ACS

AN 1999:299503 HCAPLUS

DN 130:307539

TI Human papillomavirus vectors and their use for gene therapy, hair growth, and alteration of hair color

IN Apt, Doris; Khavari, Paul; **Stemmer, William P. C.**

PA Maxygen, Inc., USA

SO PCT Int. Appl., 49 pp.

CODEN: PIXXD2

DT **Patent**

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9921979	A1	19990506	WO 1998-US22811	19981027

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9911244 A1 19990517 AU 1999-11244 19981027

PRAI US 1997-958822 19971028

WO 1998-US22811 19981027
AB The invention provides human papillomavirus vectors, which are suitable for expressing a foreign gene for use in gene therapy. Such a vector contains E1 and E2 coding regions, from a benign or low-risk human papillomavirus, and a LCR region comprising an origin of replication that includes binding sites for the E1 and E2 proteins. The vector is expressed in cutaneous epidermal cells of the patient to produce the desired protein, which may serve to compensate for a defective human gene or induce a protective immunogenic response. The invention further provides methods of using such vectors to evolve drugs for stimulation of hair growth or alteration of hair color.
RE.CNT 3
RE
(1) Medical Research Council; WO 9807876 A2 1998 HCAPLUS
(2) Pondel; Nucleic Acids Research 1992, V20(2), P237 HCAPLUS
(3) Woo; US 5674703 A 1997 HCAPLUS

L86 ANSWER 41 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:239171 HCAPLUS
TI Colorless green ideas
AU **Tobin, Matthew**; Affholter, Joseph A.; **Stemmer, Willem P. C.**; **Minshull, Jeremy**
CS Maxygen Inc., Redwood City, CA, 94063, USA
SO Nat. Biotechnol. (1999), 17(4), 333-334
CODEN: NABIF9; ISSN: 1087-0156
PB Nature America
DT Journal
LA English
AB Unavailable
RE.CNT 9
RE
(1) Cherry, J; Nat Biotechnol 1999, V17, P379 HCAPLUS
(2) Christians, F; Nat Biotechnol 1999, V17, P259 HCAPLUS
(3) Giver, L; Proc Natl Acad Sci USA 1998, V95, P12809 HCAPLUS
(4) Kumamaru, T; Nat Biotechnol 1998, V16, P663 HCAPLUS
(6) Moore, J; Nat Biotechnol 1996, V14, P458 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 42 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:164252 HCAPLUS
DN 131:231
TI Directed evolution of thymidine kinase for AZT phosphorylation using DNA family **shuffling**
AU Christians, Fred C.; Scapozza, Leonardo; Crameri, Andreas; Folkers, Gerd; **Stemmer, Willem P. C.**
CS Maxygen, Inc., Santa Clara, CA, 95051, USA
SO Nat. Biotechnol. (1999), 17(3), 259-264
CODEN: NABIF9; ISSN: 1087-0156
PB Nature America
DT Journal
LA English
AB The thymidine kinase (TK) genes from herpes simplex virus (HSV) types 1 and 2 were recombined in vitro with a technique called DNA family **shuffling**. A high-throughput robotic screen identified chimeras with an enhanced ability to phosphorylate zidovudine (AZT). Improved clones were combined, reshuffled, and screened on increasingly lower concns. of AZT. After four rounds of **shuffling** and screening, two clones were isolated that sensitize Escherichia coli to 32-fold less AZT compared with HSV-1 TK and 16,000-fold less than HSV-2 TK. Both clones are hybrids derived from several crossover events between the two parental genes and carry several addnl. amino acid substitutions not found in either parent, including active site mutations. Kinetic measurements show that the chimeric enzymes had acquired reduced KM for AZT as well as decreased specificity for thymidine. In agreement with the kinetic data, mol. modeling suggests that the active sites of both evolved enzymes better accommodate the azido group of AZT at the expense of thymidine.

Despite the overall similarity of the two chimeric enzymes, each contains key contributions from different parents in positions influencing substrate affinity. Such mutants could be useful for anti-HIV gene therapy, and similar directed-evolution approaches could improve other enzyme-prodrug combinations.

RE.CNT 33
RE
(1) Balzarini, J; Nat Med 1998, V4, P132 HCAPLUS
(2) Black, M; Biochemistry 1993, V32, P11618 HCAPLUS
(3) Black, M; Proc Natl Acad Sci USA 1996, V93, P3525 HCAPLUS
(4) Bouayadi, K; Cancer Res 1997, V57, P110 HCAPLUS
(5) Brown, D; Nat Struct Biol 1995, V2, P876 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 43 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:144094 HCAPLUS
TI Directed evolution of enzymes and pathways by DNA **shuffling**
AU **Stemmer, Willem P. C.**
CS Maxygen, Inc., Santa Clara, CA, 95051, USA
SO Book of Abstracts, 217th ACS National Meeting, Anaheim, Calif., March 21-25 (1999), BIOT-080 Publisher: American Chemical Society, Washington, D. C.
CODEN: 67GHA6
DT Conference; Meeting Abstract
LA English
AB We have developed mol. breeding formats for enzymes and metabolic pathways. Our goal is to mimic the processes used in classical breeding. An important advantage of this approach is that it does not require much prior information. DNA **shuffling** is a reliable method for homologous recombination of pools of related sequences. Libraries of chimeras are constructed from homologous DNA sequences obtained from natural diversity. The pool of the best clones obtained after one cycle of screening is re-**shuffled** to create the next library of chimeras. Screening of these libraries using a variety of high throughput anal. techniques identifies pos. combinations of sequence diversity while removing neg. combinations of sequence diversity. The application of this process to a broad range of specific examples will be described.

L86 ANSWER 44 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:672658 HCAPLUS
DN 129:271526
TI Recombination of polynucleotide sequences using random or defined primers
IN Arnold, Frances H.; Shao, Zhixin; Affholter, Joseph A.; Zhao, Huimin; **Giver, Lorraine J.**
PA California Institute of Technology, USA
SO PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9842832	A1	19981001	WO 1998-US5956	19980325
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 6153410	A	20001128	US 1997-905359	19970804
AU 9869420	A1	19981020	AU 1998-69420	19980325
AU 724698	B2	20000928		
EP 920496	A1	19990609	EP 1998-915171	19980325
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, SI, LT, LV, FI, RO

	BR 9804791	A	19990817	BR 1998-4791	19980325
	JP 2000511783	T2	20000912	JP 1998-545987	19980325
PRAI	US 1997-41666	19970325			
	US 1997-45211	19970430			
	US 1997-46256	19970512			
	US 1997-905359	19970804			
	US 1997-905058	19970801			
	WO 1998-US5956	19980325			

AB A method for in vitro mutagenesis and recombination of polynucleotide sequences based on polymerase-catalyzed extension of primer oligonucleotides is disclosed. The method involves priming template polynucleotide(s) with random-sequences or defined-sequence primers to generate a pool of short DNA fragments with a low level of point mutations. The DNA fragments are subjected to denaturization followed by annealing and further enzyme-catalyzed DNA polymn. This procedure is repeated a sufficient no. of times to produce full-length genes which comprise mutants of the original template polynucleotides. These genes can be further amplified by the polymerase chain reaction and cloned into a vector for expression of the encoded proteins. Defined flanking primers and staggered extension are used to recombine and enhance the thermostability of subtilisin E. Extended recombination primers are 1st generated by the staggered extension process, which consists of repeated cycles of denaturation followed by extremely abbreviated annealing/extension step(s). The extended fragments are reassembled into full-length genes by thermocycling-assisted homologous gene assembly in the presence of DNA polymerase, followed by an optional gene amplification step. Two thermostable subtilisin E mutants R1 and R2 were used. Among the 10 nucleotide positions that differ in R1 and R2, only those mutations leading to N181D and N218S confer thermostability.

L86 ANSWER 45 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:672568 HCAPLUS
DN 129:286711
TI Recombination of polynucleotide sequences using random or defined primers and staggered extension
IN Arnold, Frances H.; Shao, Zhixin; Affholter, Joseph A.; Zhao, Huimin; **Giver, Lorraine J.**
PA California Institute of Technology, USA
SO PCT Int. Appl., 101 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9842728	A1	19981001	WO 1998-US5814	19980325
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 6153410	A	20001128	US 1997-905359	19970804
	AU 9867725	A1	19981020	AU 1998-67725	19980325
	EP 975653	A1	20000202	EP 1998-913096	19980325
	R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE, PT, IE, FI				

PRAI	US 1997-41666	19970325
	US 1997-45211	19970430
	US 1997-46256	19970512
	US 1997-905359	19970804
	US 1997-905058	19970801
	WO 1998-US5814	19980325

AB A method for in vitro mutagenesis and recombination of polynucleotide

sequences based on polymerase-catalyzed extension of primer oligonucleotides is disclosed. The method involves priming template polynucleotide(s) with random-sequences or defined-sequence primers to generate a pool of short DNA fragments with a low level of point mutations. The DNA fragments are subjected to denaturization followed by annealing and further enzyme-catalyzed DNA polymn. This procedure is repeated a sufficient no. of times to produce full-length genes which comprise mutants of the original template polynucleotides. These genes can be further amplified by the polymerase chain reaction and cloned into a vector for expression of the encoded proteins. This method was applied to the prodn. of mutants of Bacillus subtilis subtilisin E, B. subtilis p-nitrobenzyl esterase, and Actinoplanes utahensis echinocandin B deacylase.

L86 ANSWER 46 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:623998 HCAPLUS
DN 129:240855
TI Methods for generating polynucleotides having desired characteristics by iterative selection and recombination
IN **Stemmer, Willem P. C.**; Crameri, Andreas
PA Affymax Technologies N.V., Neth. Antilles
SO U.S., 74 pp. Cont.-in-part of U.S. Ser. No. 198,431.
CODEN: USXXAM
DT **Patent**
LA English
FAN.CNT 8

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5811238	A	19980922	US 1995-564955	19951130
	US 5605793	A	19970225	US 1994-198431	19940217
	EP 934999	A1	19990811	EP 1998-122040	19950217
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
	US 5830721	A	19981103	US 1996-537874	19960304
	US 6117679	A	20000912	US 1996-621859	19960325
	CA 2239099	AA	19970605	CA 1996-2239099	19961202
	WO 9720078	A1	19970605	WO 1996-US19256	19961202
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9710873	A1	19970619	AU 1997-10873	19961202
	AU 713952	B2	19991216		
	EP 876509	A1	19981111	EP 1996-940934	19961202
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	EP 911396	A2	19990428	EP 1998-122014	19961202
	EP 911396	A3	19990506		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2000500981	T2	20000202	JP 1997-520744	19961202
	JP 2000308490	A2	20001107	JP 1999-267847	19961202
	US 6180406	B1	20010130	US 1998-99015	19980617
	AU 9923816	A1	19990812	AU 1999-23816	19990416
PRAI	US 1994-198431	19940217			
	US 1996-537874	19960304			
	AU 1995-29714	19950217			
	EP 1995-911826	19950217			
	WO 1995-US2126	19950217			
	US 1995-564955	19951130			
	US 1996-621859	19960325			
	EP 1996-940934	19961202			
	JP 1997-520744	19961202			

WO 1996-US19256 19961202

AB A method for DNA reassembly after random fragmentation, and its application to mutagenesis of nucleic acid sequences by in vitro or in vivo recombination is described. In particular, a method for the prodn. of nucleic acid fragments or polynucleotides encoding mutant proteins is described. The present invention also relates to a method of repeated cycles of mutagenesis, **shuffling** and selection which allow for the directed mol. evolution in vitro or in vivo of proteins. Using these methods, Aequorea victoria green fluorescent protein was mutagenized to a form with a 45-fold improvement in fluorescence signal. The DNA **shuffling** method, when applied to cadmium detoxification bacteria, improved cadmium resistance.

L86 ANSWER 47 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:524702 HCAPLUS
TI Directed evolution of proteins and pathways by DNA **shuffling**.
AU Affholter, Joseph; **Stemmer, Willem P. G.**
CS Maxygen, Inc., Santa Clara, CA, 95051, USA
SO Book of Abstracts, 216th ACS National Meeting, Boston, August 23-27 (1998), BIOT-042 Publisher: American Chemical Society, Washington, D. C. CODEN: 66KYA2
DT Conference; Meeting Abstract
LA English
AB We have developed directed evolution formats for single proteins, and whole metabolic pathways. Our goal is to mimic natural sexual processes, as used in traditional breeding. DNA **shuffling** or sexual PCR is a simple and reliable iterative method for homologous recombination of pools of related sequences. The initial diversity can be generated from a single sequence by point mutation and functional selection. Preferably, libraries of chimeras can be constructed from homologous sequences obtained from natural diversity. The best clones obtained after one cycle of screening are used as the starting point for the next cycle. Recombination of the pool of best sequences generates the next complex library of chimeras. Screening of these libraries using a variety of high throughput anal. techniques identifies pos. combinations of mutations while removing neg. combinations of mutations.

L86 ANSWER 48 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:509315 HCAPLUS
DN 129:132204
TI Evolution of whole cells and organisms by recursive sequence recombination
IN **Delcardayre, Stephen B.; Tobin, Mathew B.; Stemmer, Willem P. C.**; Ness, Jon E.; **Minshull, Jeremy; Patten, Phillip**
PA Maxygen, Inc., USA
SO PCT Int. Appl., 125 pp. CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9831837	A1	19980723	WO 1998-US852	19980116
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9859209	A1	19980807	AU 1998-59209	19980116
EP 1007732	A1	20000614	EP 1998-902586	19980116
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI US 1997-35054		19970117		

WO 1998-US852 19980116

AB The invention provides methods employing iterative cycles of recombination and selection/screening for evolution of whole cells and organisms toward acquisition of desired properties. Such methods entail introducing a library of DNA fragments into a plurality of cells whereby at least one of the fragments undergoes recombination with a segment in the genome or an episome of the cells to produce modified cells. The modified cells are then screened for modified cells that have evolved toward acquisition of the desired function. DNA from the modified cells that have evolved toward the desired function is then recombined with a further library of DNA fragments at least one of which undergoes recombination with a segment in the genome of the episome of the modified cells to produce further modified cells. The further modified cells are then screened for further modified cells for further modified cells that have further evolved toward acquisition of the desired function. Steps of recombination and screening/selection are repeated as required until the further modified cells have acquired the desired functions. The library or further library of DNA fragments may be coated with recA protein to stimulate recombination with the segment of the genome, and selection may be achieved by affinity chromatog. with immobilized MutS. Examples of such properties include enhanced recombinogenicity, genome copy no., and capacity for expression and/or secretion of proteins and secondary metabolites.

L86 ANSWER 49 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:509296 HCAPLUS
DN 129:133075
TI Analogs of atrazine chlorhydrolase with improved kinetic properties for use in bioremediation
IN Wackett, Lawrence P.; Sadowsky, Michael J.; De Souza, Mervyn L.; **Minshull, Jeremy S.**
PA Regents of the University of Minnesota, USA
SO PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9831816	A1	19980723	WO 1998-US944	19980116
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9860299	A1	19980807	AU 1998-60299	19980116

PRAI US 1997-35404 19970117
WO 1998-US944 19980116

AB Amino acid-substituted analogs of the atrazine chlorhydrolase of Pseudomonas ADP with improved kinetic properties and suitable for use in the remediation of contamination with s-triazines are described. The atzA and atzB genes for the enzyme were cloned by expression using degrdn. of s-atrazine as a screening assay. Mutagenesis was by recursive **shuffling** of the two genes with screening for improvement of the rate of hydrolysis of atrazine. Analogs capable of hydrolyzing terbuthylazine and melamine were also found.

L86 ANSWER 50 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:436532 HCAPLUS
DN 129:171048
TI Combinatorial protein design by in vitro recombination
AU **Giver, Lori**; Arnold, Frances H.
CS Division of Chemistry and Chemical Engineering, Institute of Technology,

Pasadena, CA, 91125, USA
SO Curr. Opin. Chem. Biol. (1998), 2(3), 335-338
CODEN: COCBF4; ISSN: 1367-5931
PB Current Biology Ltd.
DT Journal; General Review
LA English
AB A review with 26 refs. that focuses on in vitro methods for DNA recombination (often referred to as DNA **shuffling**) and application to the generation of gene libraries for directed evolution, which is a highly combinatorial approach to protein design. DNA recombination is a powerful engine for the creation of new phenotypes. Recently, methods for in vitro DNA recombination (DNA **shuffling**) have been developed and applied to the evolution of novel mols. in the lab. An exciting new development is the **shuffling** of homologous genes to create diversity for directed evolution.

L86 ANSWER 51 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:424365 HCAPLUS
DN 129:91388
TI Recursive sequence recombination and screening as a tool for the in vitro evolution of gene products
IN **Patten, Phillip A.; Stemmer, Willem P. C.**
PA Maxygen, Inc., USA; Patten, Phillip A.; Stemmer, Willem P. C.
SO PCT Int. Appl., 123 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9827230	A1	19980625	WO 1997-US24239	19971217
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9857292	A1	19980715	AU 1998-57292	19971217
EP 946755	A1	19991006	EP 1997-953571	19971217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI US 1996-769062 19961218
WO 1997-US24239 19971217
AB A method for development of proteins with new combinations of properties by recursive recombination of coding sequences of different origins and screening of gene products for desired properties is described. Recombination can be in vitro, or in vivo, e.g. using the cre/loxP system. Further variation can be introduced using mutagenesis-prone methods such as DNA repair. One method is denaturing and renaturing a population of fragments of 20-100 base pairs and selecting for those hybrids with base pair mismatches. These mismatched sequences are then ligated together to generate new sequences that will undergo DNA repair-mediated mutation. The method is flexible enough to allow coarse, or large scale, changes in sequences or it can be used at a very fine level: generating changes in a small subsequence. Many screening procedures may be used, but they must be carefully designed to detect changes of interest. Novel variants of calf intestinal alk. phosphatase with novel substrate specificity, human .alpha. interferon with higher specific activity, and luciferases with increased stability are generated.

L86 ANSWER 52 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:210853 HCAPLUS
DN 128:279557
TI Methods for optimization of gene therapy by recursive sequence

shuffling and selection
IN **Stemmer, Willem P. C.**; Christians, Frederick C.; Liu, Shi-kau
PA Maxygen, Inc., USA
SO PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9813487	A1	19980402	WO 1997-US17300	19970926
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9745037	A1	19980417	AU 1997-45037	19970926
EP 964922	A1	19991222	EP 1997-943600	19970926
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI US 1996-37742 19960927
US 1996-722660 19960927
WO 1997-US17300 19970926
AB Methods of improving the properties of DNA sequences by rounds of recombination, screening, and selection are described. **Shuffling** is achieved by taking a family of related sequences, fragmenting them, randomly re-ligating the fragments and screening the products for the desired property. Several isolates showing improvements are selected, the sequences **shuffled** again and re-screened. This process is repeated as often as needed. Mutation can be by error-prone PCR. The method can be used to improve the properties of viral and plasmid vectors. For example, vectors are evolved to have improved properties of viral titer, infectivity, expression of a gene within a vector, tissue specificity, viral genome capacity, episomal retention, lack of immunogenicity of the vectors or an expression product thereof, site-specific integration, increased stability, or capacity to confer cellular resistance to microorganism infection. The method is used to develop a novel adenovirus-based phagemid contg. the f1 origin of replication and capable of generating single-stranded DNAs of up to 10 kilobases.

L86 ANSWER 53 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:210851 HCAPLUS
DN 128:266939
TI Methods for optimization of DNA sequences for use in gene therapy by recursive sequence **shuffling** and selection
IN **Stemmer, Willem P. C.**; Van Es, Helmuth H. G.
PA Maxygen, Inc., USA; Stemmer, Willem P. C.; Van Es, Helmuth H. G.
SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9813485	A1	19980402	WO 1997-US17302	19970926
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA,				

GN, ML, MR, NE, SN, TD, TG
AU 9745971 A1 19980417 AU 1997-45971 19970926
EP 963434 A1 19991215 EP 1997-944487 19970926
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
PRAI US 1996-37742 19960927
WO 1997-US17302 19970926
AB Methods of improving the properties of DNA sequences by rounds of recombination, screening, and selection are described. **Shuffling** is achieved by taking a family of related sequences, fragmenting them, randomly re-ligating the fragments and screening the products for the desired property. Several isolates showing improvements are selected, the sequences **shuffled** again and re-screened. This process is repeated as often as needed. The method can be used to improve the properties of viral and plasmid vectors. For example, vectors are evolved to have improved properties of viral titer, infectivity, expression of a gene within a vector, tissue specificity, viral genome capacity, episomal retention, lack of immunogenicity of the vectors or an expression product thereof, site-specific integration, increased stability, or capacity to confer cellular resistance to microorganism infection. The method can also be used to modify the therapeutic gene or gene product. The method is used to develop a novel isoenzyme of O6-methylguanine-DNA methyltransferase (MGMT).

L86 ANSWER 54 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:202634 HCAPLUS
DN 128:240323
TI Peptide library and screening method
IN Schatz, Peter J.; Cull, Millard G.; Miller, Jeff F.; **Stemmer, Willem Peter Christiaan**; Gates, Christian M.
PA Affymax Technologies N.V., UK
SO U.S., 75 pp. Cont.-in-part of U.S. 5,498,530.
CODEN: USXXAM
DT **Patent**
LA English
FAN.CNT 9

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5733731	A	19980331	US 1995-548540	19951026
	US 5270170	A	19931214	US 1991-778233	19911016
	US 5338665	A	19940816	US 1992-963321	19921015
	US 5498530	A	19960312	US 1994-290641	19940815
	WO 9640987	A1	19961219	WO 1996-US9809	19960607
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM				
	AU 9663818	A1	19961230	AU 1996-63818	19960607
	EP 842293	A1	19980520	EP 1996-923256	19960607
	R: CH, DE, FR, GB, IT, LI, NL				
	US 6156511	A	20001205	US 1998-10216	19980121

PRAI US 1991-778233 19911016
US 1992-963321 19921015
US 1994-290641 19940815
US 1995-484090 19950607
US 1995-548540 19951026
WO 1996-US9809 19960607
AB A random peptide library constructed by transforming host cells with a collection of recombinant vectors that encode a fusion protein comprised of a DNA binding protein and a random peptide and also encode a binding site for the DNA binding protein can be used to screen for novel ligands. The screening method results in the formation of a complex comprising the fusion protein bound to a receptor through the random peptide ligand and to the recombinant DNA vector through the DNA binding protein. A random

peptide library is disclosed that is constructed by transforming host cells with a collection of recombinant vectors that encode a fusion protein comprised of a DNA-binding protein and a random peptide and also encode a binding site for the DNA-binding protein and that can be used to screen for novel ligands. The screening method results in the formation of a complex comprising the fusion protein bound to a receptor through the random peptide ligand and to the recombinant DNA vector through the DNA-binding protein.

L86 ANSWER 55 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:181696 HCAPLUS
DN 128:290769
TI Molecular **evolution** by **staggered** extension process (StEP) in vitro recombination
AU Zhao, Huimin; **Giver, Lori**; Shao, Zhixin; Affholter, Joseph A.; Arnold, Frances H.
CS Div. Chem. and Chem. Eng., California Inst. Technology, Pasadena, CA, 91125, USA
SO Nat. Biotechnol. (1998), 16(3), 258-261
CODEN: NABIF9; ISSN: 1087-0156
PB Nature America
DT Journal
LA English
AB We have developed a simple and efficient method for in vitro mutagenesis and recombination of polynucleotide sequences. The staggered extension process (StEP) consists of priming the template sequence(s) followed by repeated cycles of denaturation and extremely abbreviated annealing/polymerase-catalyzed extension. In each cycle the growth fragments anneal to different templates based on sequence complementarity and extend further. This is repeated until full-length sequences form. Due to template switching, most of the polynucleotides contain sequence information from different parental sequences. The method is demonstrated by the recombination of two genes encoding thermostable subtilisins carrying two phenotypic markers sepd. by 113 base pairs and eight other point mutation markers. To demonstrate its utility for directed evolution, we have used StEP to recombine a set of five thermostabilized subtilisin E variants identified during a single round of error-prone PCR mutagenesis and screening. Screening the StEP-recombined library yielded an enzyme whose half-life at 65.degree. is 50 times that of wild-type subtilisin E.

L86 ANSWER 56 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:78123 HCAPLUS
DN 128:213826
TI Random-priming in vitro recombination: an effective tool for directed **evolution**
AU Shao, Zhixin; Zhao, Huimin; **Giver, Lori**; Arnold, Frances H.
CS Division of Chemistry and Chemical Engineering 210-41, California Institute of Technology, Pasadena, CA, 91125, USA
SO Nucleic Acids Res. (1998), 26(2), 681-683
CODEN: NARHAD; ISSN: 0305-1048
PB Oxford University Press
DT Journal
LA English
AB A simple and efficient method for in vitro mutagenesis and recombination of polynucleotide sequences is reported. The method involves priming template polynucleotide(s) with random-sequence primers and extending to generate a pool of short DNA fragments which contain a controllable level of point mutations. The fragments are reassembled during cycles of denaturation, annealing and further enzyme-catalyzed DNA polymn. to produce a library of full-length sequences. Screening or selecting the expressed gene products leads to new variants with improved functions, as demonstrated by the recombination of genes encoding different thermostable subtilisins in order to obtain enzymes more stable than either parent.

L86 ANSWER 57 OF 86 HCAPLUS COPYRIGHT 2001 ACS

AN 1998:74952 HCAPLUS
DN 128:213877
TI DNA **shuffling** of a family of genes from diverse species accelerates directed evolution
AU Crameri, Andreas; Raillard, Sun-Ai; Bermudez, Ericka; **Stemmer, Willem P. C.**
CS Maxygen Inc., Santa Clara, CA, 95051, USA
SO Nature (London) (1998), 391(6664), 288-291
CODEN: NATUAS; ISSN: 0028-0836
PB Macmillan Magazines
DT Journal
LA English
AB DNA **shuffling** is a powerful process for directed evolution, which generates diversity by recombination, combining useful mutations from individual genes. Libraries of chimeric genes can be generated by random fragmentation of a pool of related genes, followed by reassembly of the fragments in a self-priming polymerase reaction. Template switching causes crossovers in areas of sequence homol. Our previous studies used single genes and random point mutations as the source of diversity. An alternative source of diversity is naturally occurring homologous genes, which provide 'functional diversity'. To evaluate whether natural diversity could accelerate the evolution process, we compared the efficiency of obtaining moxalactamase activity from four cephalosporinase genes evolved sep. with that from a mixed pool of the four genes. A single cycle of **shuffling** yielded eightfold improvements from the four sep. evolved genes, vs. a 270- to 540-fold improvement from the four genes **shuffled** together, a 50-fold increase per cycle of **shuffling**. The best clone contained eight segments from three of the four genes as well as 33 amino-acid point mutations. Mol. breeding by **shuffling** can efficiently mix sequences from different species, unlike traditional breeding techniques. The power of family **shuffling** may arise from sparse sampling of a larger portion of sequence space.

L86 ANSWER 58 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:807339 HCAPLUS
DN 128:136021
TI Applications of DNA **shuffling** to pharmaceuticals and vaccines
AU **Patten, Phillip A.**; Howard, Russell J.; **Stemmer, Willem P. C.**
CS Maxygen, Inc., Santa Clara, CA, 95051, USA
SO Curr. Opin. Biotechnol. (1997), 8(6), 724-733
CODEN: CUOBE3; ISSN: 0958-1669
PB Current Biology Ltd.
DT Journal; General Review
LA English
AB A review with 32 refs. DNA **shuffling** is a practical process for directed mol. evolution which uses recombination to dramatically accelerate the rate at which one can evolve genes. Single and multigene traits that require many mutations for improved phenotypes can be evolved rapidly. DNA **shuffling** technol. has been significantly enhanced in the past year, extending its range of applications to small mol. pharmaceuticals, pharmaceutical proteins, gene therapy vehicles and transgenes, vaccines and evolved viruses for vaccines, and lab. animal models.

L86 ANSWER 59 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:679028 HCAPLUS
DN 127:304114
TI Recursive sequence recombination including gene segment recombination and gene library screening to engineer cells for compound production, biosensors, bioremediation, or other applications
IN **Minshull, Jeremy; Stemmer, Willem P. C.**
PA Maxygen, Inc., USA; Minshull, Jeremy; Stemmer, Willem P. C.
SO PCT Int. Appl., 85 pp.
CODEN: PIXXD2

DT **Patent**
LA English
FAN.CNT 8

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9735966	A1	19971002	WO 1997-US4715	19970320
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, US, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 6117679	A	20000912	US 1996-621859	19960325
US 5837458	A	19981117	US 1996-650400	19960520
AU 9725426	A1	19971017	AU 1997-25426	19970320
EP 906418	A1	19990407	EP 1997-916943	19970320
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000507444	T2	20000620	JP 1997-534527	19970320
AU 9923816	A1	19990812	AU 1999-23816	19990416

PRAI US 1996-621430 19960325
US 1996-621859 19960325
US 1996-650400 19960520
US 1994-198431 19940217
AU 1995-29714 19950217
US 1995-425684 19950418
US 1995-564955 19951130
US 1996-537874 19960304
WO 1997-US4715 19970320

AB The present invention is generally directed to the evolution of new metabolic pathways and the enhancement of bioprocessing through a process herein termed recursive sequence recombination. Recursive sequence recombination entails performing iterative cycles of recombination and screening or selection to evolve individual genes, whole plasmids or viruses, multigene clusters, or even whole genomes. Such techniques do not require the extensive anal. and computation required by conventional methods for metabolic engineering. This invention involves recombining at least a first and second segment of a gene conferring enhanced ability to catalyze a reaction of interest to produce a library of recombinant genes. Recombinant genes are then screened from the library according to ability to catalyze the reaction of interest by the cell. The processes of gene recombination and screening are repeated until the further recombinant gene confers a desired level of enhanced ability to catalyze the reaction of interest. A further aspect of the invention is a method of evolving a biosensor for a compd. of interest by gene recombination and screening for ability to detect a compd. or related compd. The general invention is exemplified by expanding the range of substrates efficiently hydrolyzed by Escherichia coli .beta.-galactosidase. Another example is a plasmid encoding resistance to mercury salts, which after 2 rounds of recursive sequence recombination increased the tolerance of transformed Escherichia coli by a factor of 10. A third example includes recombining .beta.-lactamase genes of four different microorganisms to produce a hybrid .beta.-lactamase with 4-fold increased moxalactam resistance. And a last example is generating improved arsenate detoxification bacteria for bioremediation.

L86 ANSWER 60 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:650431 HCAPLUS
DN 127:315565
TI Evolving cellular DNA uptake by recursive sequence recombination
IN **Stemmer, Willem P. C.**
PA Maxygen, Inc., USA; Stemmer, Willem P. C.
SO PCT Int. Appl., 68 pp.
CODEN: PIXXD2

DT **Patent**
LA English
FAN.CNT 8

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9735957	A1	19971002	WO 1997-US4494	19970320
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 6096548	A	20000801	US 1997-792409	19970203
	CA 2247930	AA	19971002	CA 1997-2247930	19970320
	AU 9723377	A1	19971017	AU 1997-23377	19970320
	EP 932670	A1	19990804	EP 1997-916119	19970320
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	AU 9923816	A1	19990812	AU 1999-23816	19990416
PRAI	US 1996-621430	19960325			
	US 1997-792409	19970203			
	AU 1995-29714	19950217			
	WO 1997-US4494	19970320			

AB The invention provides a no. of strategies for transferring and/or evolving gene(s) assocd. with cellular DNA uptake so that they confer or enhance DNA-uptake capacity of a recipient cell. Evolution is achieved by recursive cycles of recombination and screening/selection. One such strategy entails evolving genes that confer competence in one species to confer either greater competence in that species, or comparable or greater competence in a second species. Another strategy entails evolving genes for use as components of a cloning vector to confer enhanced uptake of the vector. Other strategies entail evolving viral receptors, viruses, and genes that mediate conjugal transfer.

L86 ANSWER 61 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:506748 HCAPLUS
DN 127:130990
TI Staphylococcus aureus coenzyme A disulfide reductase gene sequence, enzyme inhibitors as antimicrobial agents, and infection diagnosis
IN **Delcardayre, Stephen B.**; Davies, Julian E.
PA University of British Columbia, Can.; Delcardayre, Stephen B.; Davies, Julian E.
SO PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9723628	A1	19970703	WO 1996-US20017	19961219
	W: CA, JP, MX, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2241105	AA	19970703	CA 1996-2241105	19961219
	JP 2000503530	T2	20000328	JP 1997-523747	19961219
	US 6107068	A	20000822	US 1997-886886	19970702
PRAI	US 1995-9146	19951222			
	WO 1996-US20017	19961219			

AB An isolated and purified Staphylococcus aureus CoA disulfide reductase (CoADR) is provided. Oligonucleotides encoding the CoADR, vectors and host cells contg. such oligonucleotides are also provided. In addn., antibodies reactive with the CoADR are provided, as are methods of isolating the CoADR, producing recombinant CoADR, using CoADR for screening compds. for CoADR-modulating activity, and detecting S. aureus in a test sample.

L86 ANSWER 62 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:467751 HCAPLUS
DN 127:76978
TI Methods for generating polynucleotides having desired characteristics by iterative selection and recombination
IN **Stemmer, Willem P. C.**; Crameri, Andreas
PA Affymax Technologies N.V., Neth. Antilles; Stemmer, Willem P. C.; Crameri, Andreas
SO PCT Int. Appl., 208 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 8

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9720078	A1	19970605	WO 1996-US19256	19961202
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5811238	A	19980922	US 1995-564955	19951130
US 6117679	A	20000912	US 1996-621859	19960325
AU 9710873	A1	19970619	AU 1997-10873	19961202
AU 713952	B2	19991216		
EP 876509	A1	19981111	EP 1996-940934	19961202
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000500981	T2	20000202	JP 1997-520744	19961202
AU 9923816	A1	19990812	AU 1999-23816	19990416

PRAI US 1995-564955 19951130
US 1996-621859 19960325
US 1994-198431 19940217
AU 1995-29714 19950217
US 1996-537874 19960304
WO 1996-US19256 19961202

AB A method for DNA reassembly after random fragmentation, and its application to mutagenesis of nucleic acid sequences by in vitro or in vivo recombination is described. In particular, a method for the prodn. of nucleic acid fragments or polynucleotides encoding mutant proteins is described. The present invention also relates to a method of repeated cycles of mutagenesis, **shuffling** and selection which allow for the directed mol. evolution in vitro or in vivo of proteins. Using these methods Aequoreas victorias green fluorescent protein was mutagenized to a form with a 45-fold improvement in fluorescence signal. The DNA **shuffling** method, when applied to arsenate detoxification bacteria, improved arsenate resistance 50-100-fold.

L86 ANSWER 63 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:309001 HCAPLUS
DN 127:31175
TI Directed evolution of a fucosidase from a galactosidase by DNA **shuffling** and screening
AU Zhang, Ji-Hu; Dawes, Glenn; **Stemmer, Willem P. C.**
CS Maxygen, Inc., and Affymax Research Institute, Santa Clara, CA, 95051, USA
SO Proc. Natl. Acad. Sci. U. S. A. (1997), 94(9), 4504-4509
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB An efficient .beta.-fucosidase was evolved by DNA **shuffling** from the Escherichia coli lacZ .beta.-galactosidase. Seven rounds of DNA

shuffling and colony screening on chromogenic fucose substrates were performed, using 10,000 colonies per round. Compared with native .beta.-galactosidase, the evolved enzyme purified from cells from the final round showed a 1,000-fold increased substrate specificity for o-nitrophenyl fucopyranoside vs. o-nitrophenyl galactopyranoside and a 300-fold increased substrate specificity for p-nitrophenyl fucopyranoside vs. p-nitrophenyl galactopyranoside. The evolved cell line showed a 66-fold increase in p-nitrophenyl fucosidase specific activity. The evolved fucosidase has a 10- to 20-fold increased kcat/Km for the fucose substrates compared with the native enzyme. The DNA sequence of the evolved fucosidase gene showed 13 base changes, resulting in six amino acid changes from the native enzyme. This effort shows that the library size that is required to obtain significant enhancements in specificity and activity by reiterative DNA **shuffling** and screening, even for an enzyme of 109 kDa, is within range of existing high-throughput technol. Reiterative generation of libraries and stepwise accumulation of improvements based on addn. of beneficial mutations appears to be a promising alternative to rational design.

L86 ANSWER 64 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:287884 HCAPLUS
DN 126:339366
TI Molecular evolution of an arsenate detoxification pathway by DNA **shuffling**
AU Crameri, Andreas; Dawes, Glenn; Rodriguez, Emilio, Jr.; Silver, Simon; **Stemmer, Willem P. C.**
CS Maxygen, Inc., Santa Clara, CA, 95051, USA
SO Nat. Biotechnol. (1997), 15(5), 436-438
CODEN: NABIF9; ISSN: 1087-0156
PB Nature Publishing Co.
DT Journal
LA English
AB Functional evolution of an arsenic resistance operon was accomplished by DNA **shuffling**, involving multiple rounds of in vitro recombination and mutation of a pool of related sequences, followed by selection for increased resistance in vivo. Homologous recombination is achieved by random fragmentation of the PCR templates and reassembly by primerless PCR. Plasmid-detd. arsenate resistance from plasmid pI258 encoded by genes arsR, arsB, and arsC was evolved in Escherichia coli. Three rounds of **shuffling** and selection resulted in cells that grew in up to 0.5M arsenate, a 40-fold increase in resistance. Whereas the native plasmid remained episomal, the evolved operon reproducibly integrated into the bacterial chromosome. In the absence of **shuffling**, no increase in resistance was obsd. after 4 selection cycles, and the control plasmid remained episomal. The integrated ars operon had 13 mutations. Ten mutations were located in arsB, encoding the arsenite membrane pump, resulting in a 4-6-fold increase in arsenite resistance. While arsC, the arsenate reductase gene, contained no mutations, its expression level was increased, and the rate of arsenate redn. was increased 12-fold. These results show that DNA **shuffling** can improve the function of pathways by complex and unexpected mutational mechanisms that may be activated by point mutation. These mechanisms may be difficult to explain and are likely to be overlooked by rational design.

L86 ANSWER 65 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:184613 HCAPLUS
DN 126:168826
TI Peptide library and screening method
IN Schatz, Peter J.; Cull, Millard G.; Miller, Jeff F.; **Stemmer, Willem P. C.**; Gates, Christian M.
PA Affymax Technologies N.V., UK; Schatz, Peter J.; Cull, Millard G.; Miller, Jeff F.; Stemmer, Willem P. C.; Gates, Christian M.
SO PCT Int. Appl., 150 pp.
CODEN: PIXXD2
DT **Patent**

LA English
FAN.CNT 9

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9640987	A1	19961219	WO 1996-US9809	19960607
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM				
US 5733731	A	19980331	US 1995-548540	19951026
AU 9663818	A1	19961230	AU 1996-63818	19960607
EP 842293	A1	19980520	EP 1996-923256	19960607
R: CH, DE, FR, GB, IT, LI, NL				

PRAI US 1995-484090 19950607
US 1995-548540 19951026
US 1991-778233 19911016
US 1992-963321 19921015
US 1994-290641 19940815
WO 1996-US9809 19960607

AB A random peptide library is disclosed that is constructed by transforming host cells with a collection of recombinant vectors that encode a fusion protein comprised of a DNA-binding protein and a random peptide and also encode a binding site for the DNA-binding protein and that can be used to screen for novel ligands. The screening method results in the formation of a complex comprising the fusion protein bound to a receptor through the random peptide ligand and to the recombinant DNA vector through the DNA-binding protein.

L86 ANSWER 66 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:47751 HCAPLUS
DN 126:85161
TI Preparation of second-**generation** phage libraries
AU Adey, Nils B.; **Stemmer, Willem P. C.**; Kay, Brian K.
CS Myriad Genetics, Salt Lake, UT, 84108, USA
SO Phage Disp. Pept. Proteins (1996), 277-291. Editor(s): Kay, Brian K.; Winter, Jill; McCafferty, John. Publisher: Academic, San Diego, Calif. CODEN: 63VWAU
DT Conference; General Review
LA English
AB A review with 32 refs. on making second-generation DNA libraries in phages.

L86 ANSWER 67 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1996:746344 HCAPLUS
DN 126:15518
TI Nucleic acid amplification using oligonucleotide primers with partially complementary ends
IN **Stemmer, Willem P. C.**; Lipshutz, Robert J.
PA Glaxo Group Limited, UK; Stemmer, Willem P. C.; Lipshutz, Robert J.
SO PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 8

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9633207	A1	19961024	WO 1996-US5480	19960418
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
US 5834252	A	19981110	US 1995-425684	19950418

	AU 9658509	A1	19961107	AU 1996-58509	19960418
	EP 824542	A1	19980225	EP 1996-920107	19960418
	R: CH, DE, FR, GB, IT, LI, NL				
	US 5928905	A	19990727	US 1996-675502	19960703
	AU 9923816	A1	19990812	AU 1999-23816	19990416
PRAI	US 1995-425684	19950418			
	AU 1995-29714	19950217			
	WO 1996-US5480	19960418			

AB Processes for amplifying and detecting a target nucleic acid sequence and for assembling large polynucleotides from component polynucleotides involving generating concatemers formed by PCR amplification of overlapping fragments using partially complementary primers is described. The method can form concatemers of the target sequence without the need to go through denaturation cycles either using a rolling circle replication-like mechanism or as a result of linear hybridization of single stranded ends of amplification products. By combining a no. of long, partially overlapping single-stranded DNA fragments very large sequences can be assembled. When individual sequences are presented with some base heterogeneity, multiple alleles of the target sequence can be generated in a single test tube.

L86 ANSWER 68 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1996:157006 HCAPLUS
DN 124:222054
TI Improved green fluorescent protein by molecular evolution using DNA **shuffling**
AU Crameri, Andreas; Whitehorn, Erik A.; Tate, Emily; **Stemmer, Willem P. C.**
CS Affymax Res. Inst., Palo Alto, CA, 94304, USA
SO Nat. Biotechnol. (1996), 14(3), 315-19
CODEN: NABIF9; ISSN: 1087-0156
DT Journal
LA English
AB Green fluorescent protein (GFP) has rapidly become a widely used reporter of gene regulation. However, for many organisms, particularly eukaryotes, a stronger whole cell fluorescence signal is desirable. We constructed a synthetic GFP gene with improved codon usage and performed recursive cycles of DNA **shuffling** followed by screening for the brightest E. coli colonies. A visual screen using UV light, rather than FACS selection, was used to avoid red-shifting the excitation max. After 3 cycles of DNA **shuffling**, a mutant was obtained with a whole cell fluorescence signal that was 45-fold greater than a std., the com. available Clontech plasmid pGFP. The expression level in E. coli was unaltered at about 75% of total protein. The emission and excitation maxima were also unchanged. Whereas in E. coli most of the wildtype GFP ends up in inclusion bodies, unable to activate its chromophore, most of the mutant protein is sol. and active. Three amino acid mutations appear to guide the mutant protein into the native folding pathway rather than toward aggregation. Expressed in Chinese Hamster Ovary (CHO) cells, this **shuffled** GFP mutant showed a 42-fold improvement over wildtype GFP sequence, and is easily detected with UV light in a wide range of assays. The results demonstrate how mol. evolution can solve a complex practical problem without needing to first identify which process is limiting. DNA **shuffling** can be combined with screening of a moderate no. of mutants. We envision that the combination of DNA **shuffling** and high throughput screening will be a powerful tool for the optimization of many com. important enzymes for which selections do not exist.

L86 ANSWER 69 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1996:28059 HCAPLUS
DN 124:84179
TI Construction and evolution of antibody-phage libraries by DNA **shuffling**
AU Crameri, Andreas; Cwirla, Steve; **Stemmer, Willem P. C.**
CS Affymax Res. Inst., Palo Alto, CA, 94304, USA
SO Nat. Med. (N. Y.) (1996), 2(1), 100-2

CODEN: NAMEFI; ISSN: 1078-8956
DT Journal
LA English
AB In this report, the authors describe a strategy for multistep evolution of human antibody sequences from naive libraries. The approach uses in vitro homologous recombination, termed DNA **shuffling**, for the construction of naive human antibody-phage libraries followed by the evolution of antibody sequences specific for human receptors. A stable human single-chain Fv framework (VH251-VLA25) was obtained from an Ab-phage library constructed from naive mRNA by selection for binding to diphtheria toxin. This scFv framework was used to construct a library contg. 6 synthetically mutated CDR regions based on the germline sequences. A PCR product contg. the scFv gene was randomly fragmented biol. transport DNase I digestion and the fragments reassembled by DNA **shuffling** followed by cloning into pIII of the M13 phage. The library was panned against ten human proteins; the authors focused on clones against human G-CSF receptor. After 3 to 8 rounds of selection, individual scFv phage clones exhibited an av. of 34 amino acid mutations, four of which were present in all sequences. Backcrossing of phage to remove weak mutations resulted in a halving of the no. of sequence mutations to 18. These backcrossed clones were shown to bind strongly to the G-CSF receptor, however, sol. scFv had no detectable affinity as measured by surface plasmon resonance.

L86 ANSWER 70 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:969220 HCAPLUS
DN 124:4157
TI The evolution of molecular computation
AU **Stemmer, Willem P. C.**
CS Affymax Research Inst., Palo Alto, CA, 94304, USA
SO Science (Washington, D. C.) (1995), 270(5241), 1510
CODEN: SCIEAS; ISSN: 0036-8075
DT Journal; General Review
LA English
AB A review and discussion, with 7 refs.

L86 ANSWER 71 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:934618 HCAPLUS
DN 124:1806
TI Single-step assembly of a gene and entire plasmid from large numbers of oligodeoxyribonucleotides
AU **Stemmer, Willem P. C.**; Crameri, Andreas; Ha, Kim D.; Brennan, Thomas M.; Heyneker, Herbert L.
CS Affymax Research Institute, Palo Alto, CA, 94304, USA
SO Gene (1995), 164(1), 49-53
CODEN: GENED6; ISSN: 0378-1119
DT Journal
LA English
AB Here, we describe assembly PCR as a method for the synthesis of long DNA sequences from large nos. of oligodeoxyribonucleotides (oligos). The method, which is derived from DNA **shuffling** (Stemmer, W.P.C. 1994), does not rely on DNA ligase but instead relies on DNA polymerase to build increasingly longer DNA fragments during the assembly process. A 1.1-kb fragment contg. the TEM-1 .beta.-lactamase-encoding gene (bla) was assembled in a single reaction from a total of 56 oligos, each 40 nucleotides (nt) in length. The synthetic gene was PCR amplified and cloned in a vector contg. the tetracycline-resistance gene (TcR) as the sole selectable marker. Without relying on ampicillin (Ap) selection, 76% of the TcR colonies were ApR, making this approach a general method for the rapid and cost-effective synthesis of any gene. We tested the range of assembly PCR by synthesizing, in a single reaction vessel contg. 134 oligos, a high-mol.-mass multimeric form of a 2.7-kb plasmid contg. the bla gene, the .alpha.-fragment of the lacZ gene and the pUC origin of replication. Digestion with a unique restriction enzyme, followed by ligation and transformation in Escherichia coli, yielded the correct plasmid. Assembly PCR is well suited for several in vitro mutagenesis

strategies.

L86 ANSWER 72 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:928396 HCAPLUS
DN 123:328940
TI Determination of Nekal content in aqueous solutions during its electrochemical degradation
IN Starovoitov, I. I.; **Selifonov, S. A.**; Yakubenok, E. F.; Svatikov, V. P.; Sakharovskii, V. G.; Senechkin, V. N.; Makeeva, E. N.; Belyaeva, E. N.
PA Institut Biokhimii i Fiziologii Mikroorganizmov AN SSSR, Russia; Voronezhskii Tekhnologicheskii Institut; Voronezhskii Filial Vsesoyuznogo Nauchno-Issledovatelskogo Instituta Sinteticheskogo Kauchuka
SO U.S.S.R.
From: Izobreteniya 1995, (4), 258.
CODEN: URXXAF
DT **Patent**
LA Russian
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI SU 1271216	A1	19950209	SU 1985-3853724	19850205

AB Title only translated.

L86 ANSWER 73 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:863720 HCAPLUS
DN 123:248553
TI **Shuffling** mutagenesis using pools of randomly-fragmented target DNA, PCR reassembly and in vitro and in vivo recombination in the creation of large libraries
IN **Stemmer, Willem P. C.**; Crameri, Andreas
PA Affymax Technologies N.V., Neth.
SO PCT Int. Appl., 119 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 8

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9522625	A1	19950824	WO 1995-US2126	19950217
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UG				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5605793	A	19970225	US 1994-198431	19940217
CA 2182393	AA	19950824	CA 1995-2182393	19950217
AU 9529714	A1	19950904	AU 1995-29714	19950217
AU 703264	B2	19990325		
EP 752008	A1	19970108	EP 1995-911826	19950217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1145641	A	19970319	CN 1995-191679	19950217
JP 10500561	T2	19980120	JP 1995-521977	19950217
EP 934999	A1	19990811	EP 1998-122040	19950217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
US 5830721	A	19981103	US 1996-537874	19960304
AU 9923816	A1	19990812	AU 1999-23816	19990416
PRAI US 1994-198431	19940217			
AU 1995-29714	19950217			
EP 1995-911826	19950217			
WO 1995-US2126	19950217			

AB A method for DNA reassembly after random fragmentation, and its application to mutagenesis of nucleic acid sequences by in vitro or in vivo recombination is described. In particular, a method for the prodn.

of nucleic acid fragments or polynucleotides encoding mutant proteins is described. The present invention also relates to a method of repeated cycles of mutagenesis, **shuffling** and selection which allow for the directed mol. evolution in vitro or in vivo of proteins. Randomly mutagenized incorporated into a display library may be used to select proteins with novel properties. A PCR-based reassembly of a DNase I digest of the lacZ gene with the introduction of transition and transversion mutants is demonstrated. LacZ DNA was cleaved into approx. 70 fragments with DNase I and then reassembled by PCR using a pair of primers derived from the termini of the gene. Most (84%) of the reassembled genes were LacZ+ with the LacZ- genes showing transition and transversion mutation. The reassembly method was also found to work without primers, i.e. the fragments appeared to self-prime.

L86 ANSWER 74 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:806659 HCAPLUS
DN 123:280288
TI Immobilization of biologically active molecules by changing the oxidation state of a chelated transition metal ion for affinity chromatography
IN Anderson, Leslie D.; Cook, James A.; David, Gary S.; Hochschwender, Susan M.; Kasher, Mary S.; Smith, Michele C.; **Stemmer, Willem P. C.**
PA Lilly, Eli, and Co., USA; Hybritech Inc.
SO U.S., 69 pp. Cont.-in-part of U.S. Ser. No. 647,901, abandoned.
CODEN: USXXAM
DT **Patent**
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5439829	A	19950808	US 1992-826928	19920124
	CA 2060235	AA	19920731	CA 1992-2060235	19920129
	AU 9210545	A1	19920806	AU 1992-10545	19920129
	AU 652021	B2	19940811		
	ZA 9200617	A	19930729	ZA 1992-617	19920129
	WO 9213965	A1	19920820	WO 1992-US679	19920130
	W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MW, NO, PL, RO, RU, SD				
	RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG				
	AU 9213652	A1	19920907	AU 1992-13652	19920130
	JP 06157600	A2	19940603	JP 1992-15038	19920130
PRAI	US 1991-647901	19910130			
	WO 1992-US679	19920130			

AB A chelating agent is covalently bonded to a biol. active mol. such as an enzyme or antibody, the biol. active mol. is contacted with a support contg. a bound transition metal ion whereby the metal ion is chelated by the chelating agent and the oxidn. state of the metal ion is changed by treatment with an oxidizing or a reducing agent to provide a kinetically inert oxidn. state to immobilize the biol. active mol. on the support. The transition metal ion is preferably Co(II), Cr(II) or Ru(III) and the oxidn. state of the metal ion is changed to Co(III), Cr(III) or Ru(II), resp. The chelating agent can be iminodiacetic acid (IDA), nitrilotriacetic acid, terpyridine, bipyridine, triethylenetetraamine, biethylenetriamine, 1,4,7-triazacyclonane or a chelating peptide. The chelating peptide may be incorporated into the primary structure of a protein (CP-protein) so as to provide the metal-chelating moiety, and the CP-protein may be produced by recombinant DNA technol. procedures. Certain chelating agents can immobilize more than one biol. active mol. at a metal ion site on the support. The immobilized biol. active mols. can be used in affinity chromatog. or in assay systems. CP-proteins constructed as examples include (1) the human papillomavirus type 16 E7 oncoprotein and (2) the human retinoblastoma anti-oncoprotein RB fused on their N-termini to the CP-peptide Met-His-Trp-His-His-His, (3) the CEM231.6.7 antibody pro-VH fragment possessing a His-Trp-His-His-His at the C-terminus of the VH fragment and a pro-VL fragment, and (4) the anti-CEA IgG1 heavy chain with a C-terminal peptide encoding

His-Trp-His-His-His-Pro (assembled with human .kappa.-chain VL region to form the chimeric CHEL-13 antibody). CP-E7, CP-RB, and CP-CEM were locked to a hydrophobic resin support by oxidn. of the immobilized IDA-Co(II)-CP-protein complex, whereas CHEL-13 bound to nickel-mica..

L86 ANSWER 75 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:590320 HCAPLUS
DN 123:26439
TI Searching Sequence Space
AU **Stemmer, Willem P. C.**
CS Affymax Res. Inst., Palto Alto, CA, 94304, USA
SO Bio/Technology (1995), 13(6), 549-53
CODEN: BTCHDA; ISSN: 0733-222X
DT Journal; General Review
LA English
AB A review with 27 refs.

L86 ANSWER 76 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:420777 HCAPLUS
DN 122:259843
TI Ribonuclease mutant having altered specificity
IN Raines, Ronald T.; **Del Cardayre, Stephen B.**
PA Wisconsin Alumni Research Foundation, USA
SO U.S., 10 pp.
CODEN: USXXAM
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5389537	A	19950214	US 1994-184604	19940121

AB A RNase mol. altered at a single amino acid, relative to its wild-type form, displays altered substrate specificity and substrate binding mechanism. The altered protein cleaves RNA efficiently after C, U and A residues, whereas the wild-type protein cannot cleave efficiently after A. The change that alters the specificity also permits the protein to cleave poly(A) portions of an RNA mol. processively. The bovine pancreatic RNase A (EC 3.1.27.5) was mutated at position 45 (from Thr to alanine or glycine).

L86 ANSWER 77 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:420369 HCAPLUS
DN 122:181414
TI Peptides that form homodimers or heterodimers in solution and their use in the formation of dimeric molecules
IN Aldwin, Lois; Madden, Mark; **Stemmer, W. P. C.**
PA Affymax Technologies N.V., Neth. Antilles
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9428173	A1	19941208	WO 1994-US5796	19940523
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5491074	A	19960213	US 1993-67387	19930524
AU 9470433	A1	19941220	AU 1994-70433	19940523

PRAI US 1993-67387 19930524
US 1993-43459 19930401
WO 1994-US5796 19940523

AB Peptides that form tightly assocd. homodimers or heterodimers can be used to form dimers and multimers of other mols. and mol. motifs of interest. These peptides are based on the core sequence SKVILF and can dimerize independently of other motifs added to the N- or C-terminus of the

peptide, although addns. to the C-terminus of the peptides requires the presence of certain acidic residues. These peptides can be conjugated with other peptides or to nucleic acids or carbohydrates, e.g. for affinity capture and coding sequences for these peptides can be incorporated into genes of interest. Binding characteristics of a no. of SKVILF-based peptides were detd. The strength of binding was not greatly affected by the addn. of short peptides to the N- or C-termini and the dimer was stable in urea 8M or guanidine.HCl 6M. The use of the peptide to force dimerization of the Escherichia coli maltose-binding protein is demonstrated. Analogs of the SKVILF peptide with internal amino acid substitutions that can be used in the formation of heterodimers are studied.

L86 ANSWER 78 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:173662 HCAPLUS
DN 122:24768
TI DNA **shuffling** by random fragmentation and reassembly: in vitro recombination for molecular evolution
AU **Stemmer, Willem P. C.**
CS Affymax Research Inst., Palo Alto, CA, 94304, USA
SO Proc. Natl. Acad. Sci. U. S. A. (1994), 91(22), 10747-51
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
AB Computer simulations of the evolution of linear sequences have demonstrated the importance of recombination of blocks of sequence rather than point mutagenesis alone. Repeated cycles of point mutagenesis, recombination, and selection should allow in vitro mol. evolution of complex sequences, such as proteins. A method for the reassembly of genes from their random DNA fragments, resulting in in vitro recombination is reported. A 1-kb gene, after DNase I digestion and purifn. of 10-50-bp random fragments, was reassembled to its original size and function. Similarly, a 2.7-kb plasmid could be efficiently reassembled. Complete recombination was obtained between 2 markers sepd. by 75 bp; each marker was located on a sep. gene. Oligonucleotides with 3' and 5' ends that are homologous to the gene can be added to the fragment mixt. and incorporated into the reassembled gene. Thus, mixts. of synthetic oligonucleotides and PCR fragments can be mixed into a gene at defined positions based on homol. As an example, a library of chimeras of the human and murine genes for interleukin 1.beta. was prepd. **Shuffling** can also be used for the in vitro equiv. of some std. genetic manipulations, such as a backcross with parental DNA. The advantages of recombination over existing mutagenesis methods are likely to increase with the nos. of cycles of mol. evolution.

L86 ANSWER 79 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:131155 HCAPLUS
DN 122:73962
TI Libraries of random peptide sequences and methods of screening for ligand-binding properties
IN Schatz, Peter J.; **Stemmer, Willem P. C.**
PA Affymax Technologies N.V., Neth. Antilles
SO U.S., 46 pp. Cont.-in-part of U.S. 5,270,170.
CODEN: USXXAM
DT **Patent**
LA English
FAN.CNT 9

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5338665	A	19940816	US 1992-963321	19921015
	US 5270170	A	19931214	US 1991-778233	19911016
	US 5498530	A	19960312	US 1994-290641	19940815
	US 5733731	A	19980331	US 1995-548540	19951026
	US 6156511	A	20001205	US 1998-10216	19980121
PRAI	US 1991-778233	19911016			
	US 1992-963321	19921015			

US 1994-290641 19940815
US 1995-548540 19951026

AB A random peptide library constructed by transforming host cells with a collection of expression vectors carrying chimeric genes for a fusion protein of a DNA binding protein and a random peptide and also contain a binding site for the DNA binding protein can be used to screen for novel ligands. The screening method results in the formation of a complex of the fusion protein bound to a receptor through the random peptide ligand and to the vector DNA through the DNA binding protein. The DNA encoding the peptide can therefore be immediately recovered. An expression vector for the lacI gene under control of the araB/araC system and also carrying two copies of the lacO operator was constructed by std. methods. A set of random sequences encoding dodecapeptides was cloned into an introduced SfiI site near the 3'-end of the lacI gene to generate the library. Lysates of the bank were panned for peptides binding to antibody D32.39 using antibody bound to magnetic beads. Bound DNA was recovered from the beads by phenol extn. and transformation. ELISA was used to confirm binding of the antibody by the peptide; sequencing of the random peptides and sequence searches indicated that the sequence recognized by the antibody was from a dynorphin B.

L86 ANSWER 80 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1994:597005 HCAPLUS
DN 121:197005
TI Rapid evolution of a protein in vitro by DNA **shuffling**
AU **Stemmer, Willem P. C.**
CS Affymax Research Institute, Palo Alto, CA, 94304, USA
SO Nature (London) (1994), 370(6488), 389-91
CODEN: NATUAS; ISSN: 0028-0836
DT Journal
LA English
AB DNA **shuffling** is a method for in vitro homologous recombination of pools of selected mutant genes by random fragmentation and polymerase chain reaction (PCR) reassembly. Computer simulations called genetic algorithms have demonstrated the importance of iterative homologous recombination for sequence evolution. Oligonucleotide cassette mutagenesis and error-prone PCR are not combinatorial and thus are limited in searching sequence space. We have tested mutagenic DNA **shuffling** for mol. evolution in a .beta.-lactamase model system. Three cycles of **shuffling** and two cycles of backcrossing with wild-type DNA, to eliminate non-essential mutations, were each followed by selection on increasing concns. of the antibiotic cefotaxime. We report here that selected mutants had a min. inhibitory concn. of 640 .mu.g mL-1, a 32,000-fold increase and 64-fold greater than any published TEM-1 derived enzyme. Cassette mutagenesis and error-prone PCR resulted in only a 16-fold increase.

L86 ANSWER 81 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1993:510564 HCAPLUS
DN 119:110564
TI Enzymatic inverse polymerase chain reaction library mutagenesis
IN **Stemmer, Willem P. C.**
PA Hybritech Inc., USA
SO PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9312257	A1	19930624	WO 1992-US10647	19921210
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9332747	A1	19930719	AU 1993-32747	19921210
US 5514568	A	19960507	US 1994-184751	19940119
US 5512463	A	19960430	US 1994-252057	19940601

PRAI US 1991-806154 19911212
US 1991-691140 19910426
WO 1992-US10647 19921210

AB The title method for introducing mutations into a desired region of a double-stranded nucleic acid is claimed. The method comprises provided a 1st and 2nd primer population, each population having a variable base compn. at known positions, and each incorporating a class IIS restriction enzyme cleavage site. The 2 primer populations are hybridized to opposite strands of the target nucleic acid to form pairs of primers oriented in opposite directions. The enzymic inverse PCR is performed to produce a linear copy of mutant double-stranded nucleic acid, and the nucleic acids are cleaved with a class IIS restriction enzyme. The complementary ends of the nucleic acid are ligated and the resulting nucleic acid is introduced into appropriate host cells. The method was used to create a plasmid contg. a gene for a single-chain Fv protein from a plasmid contg. sep. genes for the heavy and light chain V regions.

L86 ANSWER 82 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1993:402474 HCAPLUS
DN 119:2474
TI Construction of peptide library and its use in screening for receptor ligands
IN Schatz, Peter J.; Cull, Millard G.; Miller, Jeff F.; **Stemmer, Willem Peter Christian**
PA Affymax Technologies N. V., Neth.
SO PCT Int. Appl., 153 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 9

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9308278	A1	19930429	WO 1992-US8879	19921015
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE				
US 5270170	A	19931214	US 1991-778233	19911016
AU 9337596	A1	19930521	AU 1993-37596	19921015
EP 610448	A1	19940817	EP 1993-908777	19921015
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, SE				

PRAI US 1991-778233 19911016
WO 1992-US8879 19921015

AB A method of constructing a random peptide library comprises prepg. a DNA vector contg. a gene for a DNA binding protein and a binding site for that protein. The vector is modified by insertion of coding sequences for random peptides into the DNA binding protein gene such that fusion proteins are encoded. Host cells are transformed with these vectors and cultured to produce the fusion proteins. To screen the peptide library, the cells are lysed under conditions allowing the fusion protein to remain bound to the vector encoding the fusion protein, and the lysate is contacted with an (immobilized) receptor. This screening process can be repeated. Plasmid pMC5, contg. 2 lacOs sequences and a lacI gene, was prepd. and oligonucleotides encoding random dodecamers were inserted. These chimeric lacI genes were expressed in Escherichia coli and the fusion proteins in E. coli lysates were screened with anti-dynorphin antibody. Over 50 ligands were identified in this manner and their sequences were detd. by plasmid sequencing.

L86 ANSWER 83 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1993:117660 HCAPLUS
DN 118:117660
TI Increased antibody expression from Escherichia coli through **wobble** -base library mutagenesis by enzymic inverse PCR
AU **Stemmer, Willem P. C.**; Morris, Suzanne K.; Kautzer, Curtis R.; Wilson, Barry S.
CS Ther. Dep., Hybritech, Inc., San Diego, CA, 92196-9006, USA
SO Gene (1993), 123(1), 1-7

CODEN: GENED6; ISSN: 0378-1119
DT Journal
LA English
AB The value of a new library mutagenesis approach, called library enzymic inverse PCR (LEIPCR), was tested for expression-level enhancement of antibody Fv fragments produced in Escherichia coli. The prodn. level of active, metal chelate-specific antibody was limited by a low expression level of the second, heavy-chain cistron. To increase the prodn. level, LEIPCR was applied to the wobble bases of the second cistron leader peptide. In LEIPCR mutagenesis, the entire plasmid is amplified using mutagenic primers with class-IIS restriction endonuclease (ENase) sites at their 5' ends. The PCR product is digested with the class-IIS ENase (here, BsaI; GGTCTCN .dwnarw.NNNN.uparw.), which removes its own recognition sequence, and the ends are self-ligated. Thus, LEIPCR can be used to make plasmid mutant libraries regardless of the nucleotide sequence, and independent of available ENase sites. The resulting library of 107 wobble mutants was screened for active Fv by a colony filter lift. A selected mutant was shown to produce 4-11-fold more active Fv than the wild type (wt), and 5-fold more heavy chain. Mutations outside of the leader peptide were shown not to be involved. The mutated areas of the mRNAs of two different up-mutants may have less secondary structure than the wt. Thus, the sequence of the mRNA of the second leader peptide was limiting to the expression level of heavy-chain and active Fv.

L86 ANSWER 84 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1993:97582 HCAPLUS
DN 118:97582
TI Method of immobilizing and crosslinking proteins and other molecules and uses thereof
IN Anderson, Leslie Deriemer; Cook, James Allen; David, Gary Samuel; Hochschwender, Susan Marie; Kasher, Mary Seybold; Smith, Michele Ceceil; **Stemmer, William Peter Christian**
PA USA
SO Eur. Pat. Appl., 88 pp.
CODEN: EPXXDW
DT **Patent**
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 497585	A2	19920805	EP 1992-300775	19920130
EP 497585	A3	19930505		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, PT, SE				
CA 2060235	AA	19920731	CA 1992-2060235	19920129
AU 9210545	A1	19920806	AU 1992-10545	19920129
AU 652021	B2	19940811		
ZA 9200617	A	19930729	ZA 1992-617	19920129
WO 9213965	A1	19920820	WO 1992-US679	19920130
W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MW, NO, PL, RO, RU, SD				
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG				
AU 9213652	A1	19920907	AU 1992-13652	19920130
JP 06157600	A2	19940603	JP 1992-15038	19920130
PRAI US 1991-647901	19910130			
WO 1992-US679	19920130			

AB A method is disclosed for immobilizing and purifying proteins. Also provided is a method for the formation of a kinetically inert complex between a transition metal ion and a biol. active mol. or reporter group which possesses a metal binding site to form a kinetically inert complex between the CP-protein (CP = chelating peptide) and the bound metal ion. This kinetically inert (immobilized metal/CP-protein) complex provides a component of an assay system useful for studying the interaction of any of a variety of ligands with the immobilized CP-protein. Also provided is a method of purifying immunoreactive proteins (IPs; antibodies, antibody fragments, etc.) or receptors on a solid support. Immobilization of IPs

or other biol. active mols. using the methodol. of the invention enables the orientation of the mols. so as to maximize exposure of the antigen or ligand binding site in an affinity chromatog. system. Further provided is a method of forming heterodimeric, homodimeric, or multimeric complexes by crosslinking .gtoreq.2 biol. active mols. or reporter groups with metal binding sites. Thus, plasmid p16E7e was constructed and expressed in Escherichia coli for the prodn. of a fusion product contg. the human papillomavirus 16 E7 oncoprotein sequence and a CP (Met-His-Trp-His-His-His) sequence. The protein was immobilized on a Co(II)-IDA-resin (IDA = iminodiacetic acid), and the resulting kinetically labile resin was converted to the corresponding kinetically inert resin by oxidn. of the Co(II) to Co(III). The resin bound RB (anti-oncoprotein derived from human retinoblastoma gene) specifically, and the binding could be diminished by competition with excess free E7 or CP-E7. Prepn. of an anti-carcinoembryonic antigen antibody construct contg. a CP, and immobilization of the antibody onto a Ni-mica surface via the CP, are also described.

L86 ANSWER 85 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1992:1741 HCAPLUS
DN 116:1741
TI Construction of expression cassettes for the isopenicillin N epimerase gene of Streptomyces clavuligerus
IN Kovacevic, Steven; Miller, James Robert; Skatrud, Paul Luther; **Tobin, Matthew Barry**
PA Lilly, Eli, and Co., USA
SO Eur. Pat. Appl., 41 pp.
CODEN: EPXXDW
DT **Patent**
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 377295	A1	19900711	EP 1989-313150	19891215
	EP 377295	B1	19950201		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, NL, SE				
	CA 2005649	AA	19900622	CA 1989-2005649	19891215
	ES 2067556	T3	19950401	ES 1989-313150	19891215
	DK 8906414	A	19900623	DK 1989-6414	19891218
	AU 8947098	A1	19900628	AU 1989-47098	19891221
	AU 622253	B2	19920402		
	HU 53149	A2	19900928	HU 1989-6734	19891221
	HU 208713	B	19931228		
	JP 02227082	A2	19900910	JP 1989-334675	19891222
PRAI	US 1988-288760		19881222		

AB The isopenicillin N epimerase (I) gene of Streptomyces clavuligerus is modified to allow it to be inserted into expression vectors for a variety of prokaryotic and eukaryotic hosts. Site-directed mutagenesis was used to convert the sequence surrounding the initiator ATG to an NcoI site. This gene could then be cloned into an appropriate expression cassette without extraneous sequences. This modified gene was then cloned into expression cassettes for Escherichia coli and Penicillium (using the promoter for the corresponding gene from Penicillium). Transformants of E. coli were shown to be able to interconvert penicillin N and isopenillin N and to produce material cross-reacting with antibodies to I that detected a band of .apprx.50,000 mol.-wt. on Western blots.

L86 ANSWER 86 OF 86 HCAPLUS COPYRIGHT 2001 ACS
AN 1991:486735 HCAPLUS
DN 115:86735
TI Vectors for the expression of the isopenicillin N acyltransferase gene of Aspergillus nidulaus
IN Miller, James Robert; Skatrud, Paul Luther; **Tobin, Matthew Barry**
PA Lilly, Eli, and Co., USA
SO Eur. Pat. Appl., 56 pp.
CODEN: EPXXDW

DT **Patent**
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 422790	A2	19910417	EP 1990-310448	19900925
	EP 422790	A3	19910821		
	EP 422790	B1	19960313		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE				
	IL 95766	A1	19961205	IL 1990-95766	19900924
	AT 135399	E	19960315	AT 1990-310448	19900925
	ES 2086374	T3	19960701	ES 1990-310448	19900925
	CA 2026262	AA	19910328	CA 1990-2026262	19900926
	JP 03133384	A2	19910606	JP 1990-260282	19900927
PRAI	US 1989-413401	19890927			

AB The isopenicillin N:acylCoA acyltransferase (I) gene of Aspergillus nidulans is expressed in bacteria and filamentous fungi. High-level expression of this gene in such organisms is used to affect the repertoire of .beta.-lactam antibiotics manufd. by them. A plasmid encoding I expressed from the isopenicillin N synthase gene promoter of Penicillium chrysogenum was constructed by std. methods and transformed into A. nidulans. The use of the cloned I gene for disruption of the endogenous gene and the use of antisense transcripts are also discussed. Organisms lacking I activity can be used to manuf. cephalosporins after introduction of genes for cephalosporin biosynthesis.

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L110 ANSWER 1 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:506209 BIOSIS
DN PREV200000506209
TI Improving HIV-1 replication on pigtailed macaque PBMCs by **DNA shuffling**.
AU Pekrun, Katja; Sheppard, Liana T.; Reed, Margaret; Shibata, Riri; **Stemmer, Willem**; Soong, Nay-Wei
SO Journal of Human Virology, (September October, 2000) Vol. 3, No. 5, pp. 276. print.
Meeting Info.: **2000 International Meeting of the Institute of Human Virology** Baltimore, Maryland, USA September 10-15, 2000
ISSN: 1090-9508.
DT **Conference**
LA English
SL English
CC Immunology and Immunochemistry - General; Methods *34502
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - General *03502
Genetics and Cytogenetics - Animal *03506
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biochemical Studies - Proteins, Peptides and Amino Acids *10064

Blood, Blood-Forming Organs and Body Fluids - Blood and Lymph Studies *15002
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
Genetics of Bacteria and Viruses *31500
Virology - Animal Host Viruses *33506
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
Medical and Clinical Microbiology - Virology *36006
BC Retroviridae 02623
IT Major Concepts
Molecular Genetics (Biochemistry and Molecular Biophysics); Infection; Blood and Lymphatics (Transport and Circulation)
IT Parts, Structures, & Systems of Organisms
peripheral blood mononuclear cells: blood and lymphatics, immune system
IT Diseases
AIDS [acquired immunodeficiency syndrome]: immune system disease, viral disease; HIV-1 infection [human immunodeficiency virus 1 infection]: immune system disease, viral disease
IT Chemicals & Biochemicals
DNA; proteins
IT Alternate Indexing
Acquired Immunodeficiency Syndrome (MeSH); HIV Infections (MeSH)
IT Methods & Equipment
DNA shuffling: molecular genetic method
IT Miscellaneous Descriptors
molecular **evolution** technology; **recombination**; viral pathogenesis; viral replication: analysis, improvement; **Meeting Abstract**
ORGN Super Taxa
Cercopithecidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Retroviridae: Animal Viruses, Viruses, Microorganisms
ORGN Organism Name
HIV-1 [human immunodeficiency virus 1] (Retroviridae): pathogen; pigtailed macaque (Cercopithecidae): animal model, host
ORGN Organism Superterms
Animal Viruses; Animals; Chordates; Mammals; Microorganisms; Nonhuman Mammals; Nonhuman Primates; Nonhuman Vertebrates; Primates; Vertebrates; Viruses

L110 ANSWER 2 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:179714 BIOSIS
DN PREV200000179714
TI Generating new biocatalysts by Molecular **Breeding**.
AU **delCardayre, Stephen B. (1)**; Zhang, Ying-Xin (1); Huisman, Gjalt W. (1)
CS (1) Maxygen, Inc, 515 Galveston Dr, Redwood City, CA, 94063 USA
SO Abstracts of Papers American Chemical Society, (2000) Vol. 219, No. 1-2, pp. BIOT 88.
Meeting Info.: **219th Meeting of the American Chemical Society**. San Francisco, California, USA March 26-30, 2000 American Chemical Society . ISSN: 0065-7727.
DT **Conference**
LA English
SL English
CC **Biochemical Methods - Proteins, Peptides and Amino Acids *10054**
Evolution *01500
Genetics and Cytogenetics - General *03502
Comparative Biochemistry, General *10010
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Bioengineering *10511
Metabolism - Energy and Respiratory Metabolism *13003
Metabolism - Proteins, Peptides and Amino Acids *13012
Metabolism - General Metabolism; Metabolic Pathways *13002
Biophysics - Molecular Properties and Macromolecules *10506
Biochemical Studies - General *10060
Biochemical Methods - General *10050

General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
IT Major Concepts
Molecular Genetics (Biochemistry and Molecular Biophysics); Bioprocess Engineering; Methods and Techniques
IT Chemicals & Biochemicals
polypeptides: design; proteins: expression, functions
IT Methods & Equipment
directed **evolution**: molecular genetic method; molecular **breeding**: molecular genetic method
IT Miscellaneous Descriptors
biocatalysts: applications, **generation**, new; biotechnology; fermentation processes; genomes; metabolic pathways: regulation; **Meeting Abstract**

L110 ANSWER 3 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:167306 BIOSIS
DN PREV200000167306
TI Molecular **breeding** of genes, pathways, and genomes by **DNA shuffling.**
AU **Stemmer, Willem P. C. (1)**
CS (1) Maxygen, Inc, 515 Galveston Drive, Redwood City, CA, 94063 USA
SO Abstracts of Papers American Chemical Society., (2000) Vol. 219, No. 1-2, pp. AGFD 104.
Meeting Info.: **219th Meeting of the American Chemical Society.** San Francisco, California, USA March 26-30, 2000 American Chemical Society . ISSN: 0065-7727.
DT **Conference**
LA English
SL English
CC **Genetics and Cytogenetics - Animal *03506**
Biochemical Studies - General *10060
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
BC Microorganisms - Unspecified 01000
IT Major Concepts
Molecular Genetics (Biochemistry and Molecular Biophysics); Methods and Techniques; Microbiology
IT Methods & Equipment
DNA shuffling: genetic **recombination** method; molecular **breeding** format: biochemical method
IT Miscellaneous Descriptors
Meeting Abstract
ORGN Super Taxa
Microorganisms; Viruses: Microorganisms
ORGN Organism Name
microbe (Microorganisms); virus (Viruses)
ORGN Organism Superterms
Microorganisms; Viruses

L110 ANSWER 4 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:455175 BIOSIS
DN PREV199900455175
TI Directed **evolution** of mesophilic enzymes into their thermophilic counterparts.
AU Arnold, Frances H. (1); **Giver, Lori**; Gershenson, Anne; Zhao, Huimin; Miyazaki, Ken
CS (1) Division of Chemistry and Chemical Engineering, California Institute of Technology 210-41, Pasadena, CA, 91125 USA
SO Caporale, L. H. [Editor]. Annals of the New York Academy of Sciences, (May 18, 1999) Vol. 870, pp. 400-403. Annals of the New York Academy of Sciences; Molecular strategies in biological evolution.
Publisher: New York Academy of Sciences 2 East 63rd Street, New York, New York 10021, USA.
Meeting Info.: **Conference** New York, New York, USA June 27-29, 1998 New York Academy of Sciences

. ISSN: 0077-8923. ISBN: 1-57331-192-8 (cloth), 1-57331-193-6 (paper).
DT Book; **Conference**
LA English
CC Enzymes - Chemical and Physical *10806
Evolution *01500
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Physiology and Biochemistry of Bacteria *31000
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics)
IT Chemicals & Biochemicals
Bacillus subtilis p-nitrobenzyl esterase: directed **evolution**, mesophilic enzyme; Bacillus subtilis subtilisin E: directed **evolution**, mesophilic enzyme; Bacillus subtilis thermitase: subtilisin E thermophilic homolog
IT Miscellaneous Descriptors
molecular **evolution**; Book Chapter; **Meeting** Paper; **Meeting Poster**

L110 ANSWER 5 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:324115 BIOSIS
DN PREV199900324115
TI **DNA shuffling** of diverse natural genes to produce industrial enzymes with novel properties.
AU Welch, M. (1); Ness, J. (1); **Stemmer, W.P.C. (1)**; **Minshull, J. (1)**
CS (1) Maxygen, Santa Clara, CA USA
SO **Abstracts of the General Meeting of the American Society for Microbiology**, (1999) Vol. 99, pp. 507-508.
Meeting Info.: **99th General Meeting of the American Society for Microbiology** Chicago, Illinois, USA May 30-June 3, 1999 American Society for Microbiology
. ISSN: 1060-2011.
DT **Conference**
LA English
CC Enzymes - General and Comparative Studies; Coenzymes *10802
Genetics and Cytogenetics - General *03502
Biochemical Methods - General *10050
Biochemical Methods - Nucleic Acids, Purines and Pyrimidines *10052
Biochemical Studies - General *10060
Metabolism - General Metabolism; Metabolic Pathways *13002
Food and Industrial Microbiology - General and Miscellaneous *39008
Replication, Transcription, Translation *10300
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Methods - Proteins, Peptides and Amino Acids *10054
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
BC Microorganisms - Unspecified 01000
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Molecular Genetics (Biochemistry and Molecular Biophysics)
IT Chemicals & Biochemicals
industrial enzymes: molecular properties, production; **recombinant** enzymes: production; **DNA**
IT Miscellaneous Descriptors
diverse natural genes; **DNA shuffling**; **Meeting Abstract**; **Meeting Poster**
ORGN Super Taxa
Microorganisms
ORGN Organism Name
microorganisms (Microorganisms)
ORGN Organism Superterms
Microorganisms

L110 ANSWER 6 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:304826 BIOSIS
DN PREV199900304826
TI Directed **evolution** of enzymes and pathways by **DNA shuffling**.
AU **Stemmer, Willem P. C. (1)**
CS (1) Maxygen, Inc., 3410 Central Expressway, Santa Clara, CA, 95051 USA
SO FASEB Journal, (April 23, 1999) Vol. 13, No. 7, pp. A1431.
Meeting Info.: **Annual Meeting of the American Societies for Experimental Biology on Biochemistry and Molecular Biology 99** San Francisco, California, USA May 16-20, 1999 American Societies for Experimental Biology
. ISSN: 0892-6638.
DT **Conference**
LA English
CC **Genetics and Cytogenetics - General *03502**
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Enzymes - General and Comparative Studies; Coenzymes *10802
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
IT Major Concepts
Methods and Techniques; Molecular Genetics (Biochemistry and Molecular Biophysics)
IT Chemicals & Biochemicals
enzymes: directed **evolution**
IT Methods & Equipment
DNS **shuffling**: molecular genetic method
IT Miscellaneous Descriptors
metabolic pathways: directed **evolution**; molecular **breeding**; **Meeting Abstract**

L110 ANSWER 7 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:166965 BIOSIS
DN PREV199900166965
TI Directed **evolution** of enzymes and pathways by **DNA shuffling**.
AU **Stemmer, Willem P. C. (1)**
CS (1) Maxygen Inc., 3410 Central Expressway, Santa Clara, CA 95051 USA
SO Abstracts of Papers American Chemical Society, (1999) Vol. 217, No. 1-2, pp. BIOT 080.
Meeting Info.: **217th National Meeting of the American Chemical Society** Anaheim, California, USA March 21-25, 1999 American Chemical Society
. ISSN: 0065-7727.
DT **Conference**
LA English
CC **Genetics and Cytogenetics - General *03502**
Biochemical Methods - General *10050
Biophysics - General Biophysical Studies *10502
Enzymes - General and Comparative Studies; Coenzymes *10802
Food and Industrial Microbiology - General and Miscellaneous *39008
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
BC Organisms - Unspecified 00500
IT Major Concepts
Bioprocess Engineering; Molecular Genetics (Biochemistry and Molecular Biophysics)
IT Chemicals & Biochemicals
enzymes; **DNA**
IT Methods & Equipment
DNA shuffling: directed **evolution** method, molecular genetic method
IT Miscellaneous Descriptors
Meeting Abstract
ORGN Super Taxa

Organisms
ORGN Organism Name
organism (Organisms)

L110 ANSWER 8 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:153847 BIOSIS
DN PREV199900153847
TI Directed **evolution** of a thermophilic esterase.
AU Gershenson, Anne; **Giver, Lori**; Arnold, Frances H.
CS Div. Chem. Chemical Eng., Calif. Inst. Technol., Pasadena, CA 91125 USA
SO Abstracts of Papers American Chemical Society, (1999) Vol. 217, No. 1-2, pp. BIOT 104.
Meeting Info.: **217th National Meeting of the American Chemical Society** Anaheim, California, USA March 21-25, 1999 American Chemical Society
. ISSN: 0065-7727.
DT **Conference**
LA English
CC Enzymes - General and Comparative Studies; Coenzymes *10802
Evolution *01500
Genetics and Cytogenetics - General *03502
Comparative Biochemistry, General *10010
Biochemical Methods - General *10050
Biochemical Studies - General *10060
Biophysics - Molecular Properties and Macromolecules *10506
External Effects - Temperature as a Primary Variable - Hot *10618
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Methods and Techniques
IT Chemicals & Biochemicals
thermophilic esterases: applications, enzymatic properties, kinetics, molecular characteristics
IT Methods & Equipment
directed **evolution**: molecular genetic method; **protein engineering**: molecular genetics/genetic engineering, synthetic method
IT Miscellaneous Descriptors
biotechnology; enzyme design; **Meeting Abstract**
RN 9013-79-0 (ESTERASE)
9013-79-0D (ESTERASES)

L110 ANSWER 9 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:422095 BIOSIS
DN PREV199800422095
TI Directed **evolution** of proteins and pathways by **DNA shuffling**.
AU Affholter, Joseph; **Stemmer, Willem P. C.**
CS Maxygen Inc., 3410 Central Expressway, Santa Clara, CA 95051 USA
SO Abstracts of Papers American Chemical Society, (1998) Vol. 216, No. 1-3, pp. BIOT 42.
Meeting Info.: **216th National Meeting of the American Chemical Society** Boston, Massachusetts, USA August 23-27, 1998 American Chemical Society
. ISSN: 0065-7727.
DT **Conference**
LA English
CC **Genetics and Cytogenetics - General *03502**
Biochemical Studies - General *10060
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
IT Major Concepts
Evolution and Adaptation; Genetics
IT Miscellaneous Descriptors
direct protein **evolution**; protein pathway **evolution**

; **DNA shuffling; Meeting Abstract**

L110 ANSWER 10 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:330867 BIOSIS
DN PREV199800330867
TI Directed **evolution** of proteins, pathways, episomes and viruses by **DNA shuffling.**
AU **Stemmer, Willem P. C. (1)**
CS (1) Maxygen Inc., 3410 Central Expressway, Santa Clara, CA 95051 USA
SO FASEB Journal, (April 24, 1998) Vol. 12, No. 8, pp. A1303.
Meeting Info.: **Meeting of the American Society for Biochemistry and Molecular Biology** Washington, D.C., USA May 16-20, 1998 American Society for Biochemistry and Molecular Biology
. ISSN: 0892-6638.
DT **Conference**
LA English
CC Enzymes - Methods *10804
Genetics and Cytogenetics - General *03502
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Virology - General; Methods *33502
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
BC Viruses - General 02500
IT Major Concepts
Methods and Techniques; Molecular Genetics (Biochemistry and Molecular Biophysics)
IT Chemicals & Biochemicals
protein
IT Methods & Equipment
DNA shuffling [sexual **PCR**]: analytical method
IT Miscellaneous Descriptors
directed **evolution**; episome; **Meeting Abstract**
ORGN Super Taxa
Viruses: Microorganisms
ORGN Organism Name
virus (Viruses)
ORGN Organism Superterms
Microorganisms; Viruses

L110 ANSWER 11 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:420823 BIOSIS
DN PREV199799720026
TI Molecular **evolution** of genes and pathways by **DNA shuffling.**
AU **Stemmer, W. P. C.**; Crameri, A.; Minshull, I.
CS Maxygen, 3410 Central Expressway, Santa Clara, CA 95051 USA
SO FASEB Journal, (1997) Vol. 11, No. 9, pp. A1124.
Meeting Info.: **17th International Congress of Biochemistry and Molecular Biology in conjunction with the Annual Meeting of the American Society for Biochemistry and Molecular Biology** San Francisco, California, USA August 24-29, 1997
ISSN: 0892-6638.
DT **Conference; Abstract**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Genetics and Cytogenetics - General *03502
Biochemical Methods - Nucleic Acids, Purines and Pyrimidines *10052
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biophysics - General Biophysical Techniques *10504

IT Major Concepts
Biochemistry and Molecular Biophysics; Genetics; Methods and Techniques
IT Miscellaneous Descriptors
DNA SHUFFLING; GENETIC METHOD; MOLECULAR **EVOLUTION**; MOLECULAR GENETICS; PATHWAYS

L110 ANSWER 12 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:98184 BIOSIS
DN PREV199799397387
TI Purification of poly(His)-tagged **recombinant** proteins using HisTrap.
AU Heijbel, A.; Andersson, K.; Carlsson, M.; **Gustafsson, C.**
CS Pharmacia Biotech AB, S-751 82 Uppsala Sweden
SO Molecular Biology of the Cell, (1996) Vol. 7, No. SUPPL., pp. 668A.
Meeting Info.: **Annual Meeting of the 6th International Congress on Cell Biology and the 36th American Society for Cell Biology** San Francisco, California, USA December 7-11, 1996
ISSN: 1059-1524.
DT **Conference; Abstract; Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Methods - Proteins, Peptides and Amino Acids *10054
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - General Biophysical Techniques *10504
IT Major Concepts
Biochemistry and Molecular Biophysics; Methods and Techniques
IT Miscellaneous Descriptors
HISTRAP PURIFICATION KIT; METHODOLOGY; POLY(HIS)-TAGGED **RECOMBINANT** PROTEIN; POLY(HISTIDINE)-TAGGED **RECOMBINANT** PROTEIN; PROTEIN BINDING CAPACITY; PURIFICATION METHOD

L110 ANSWER 13 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:308207 BIOSIS
DN PREV199699030563
TI Purification of poly(his)-tagged **recombinant** proteins using HisTrap.
AU Heijbel, A.; Andersson, K.; Bell, P.; **Gustafsson, C.**
CS Pharmacia Biotech AB, S-751 82 Uppsala Sweden
SO FASEB Journal, (1996) Vol. 10, No. 6, pp. A1127.
Meeting Info.: **Joint Meeting of the American Society for Biochemistry and Molecular Biology, the American Society for Investigative Pathology and the American Association of Immunologists** New Orleans, Louisiana, USA June 2-6, 1996
ISSN: 0892-6638.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Genetics and Cytogenetics - General *03502
Biochemical Methods - Proteins, Peptides and Amino Acids *10054
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - General Biophysical Techniques *10504
IT Major Concepts
Biochemistry and Molecular Biophysics; Genetics; Methods and Techniques
IT Miscellaneous Descriptors
MEETING ABSTRACT; PROTEIN ENGINEERING; PURIFICATION METHOD; **RECOMBINANT DNA** TECHNOLOGY

L110 ANSWER 14 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:252019 BIOSIS
DN PREV199698808148
TI **DNA** sequence **evolution** by sexual **PCR**.

AU **Stemmer, Willem P. C.**
CS Affymax Res. Inst., Palo Alto, CA 94304 USA
SO Experientia (Basel), (1996) Vol. 52, No. ABSTR., pp. A25.
Meeting Info.: **28th Annual Meeting of the Swiss Societies for Experimental Biology (USGEB/USSBE)** Zuerich-Irchel, Switzerland March 27-29, 1996
ISSN: 0014-4754.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Evolution *01500
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Genetics of Bacteria and Viruses *31500
BC Enterobacteriaceae *06702
IT Major Concepts
Biochemistry and Molecular Biophysics; **Evolution** and Adaptation; Genetics
IT Miscellaneous Descriptors
DNA SHUFFLING; MEETING ABSTRACT ; POLYMERASE CHAIN REACTION
ORGN Super Taxa
Enterobacteriaceae: Eubacteria, Bacteria
ORGN Organism Name
Escherichia coli (Enterobacteriaceae)
ORGN Organism Superterms
bacteria; eubacteria; microorganisms

L110 ANSWER 15 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1994:334216 BIOSIS
DN PREV199497347216
TI Selecting aptamers for nucleic acid binding proteins: A call to "**ARM**"s.
AU Ellington, Andrew D. (1); **Giver, Lorraine J. (1)**; Baskerville, D. Scott (1); Kumar, P. K. R. (1); Leclerc, Fabrice; Cedergren, Robert; Zapp, Maria (1)
CS (1) Dep. Chem., Indiana Univ., Bloomington, IN 47405 USA
SO FASEB Journal, (1994) Vol. 8, No. 7, pp. A1325.
Meeting Info.: **85th Annual Meeting of the American Society for Biochemistry and Molecular Biology** Washington, D.C., USA May 21-25, 1994
ISSN: 0892-6638.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
IT Major Concepts
Biochemistry and Molecular Biophysics
IT Chemicals & Biochemicals
ARGININE
IT Miscellaneous Descriptors
ARGININE-RICH MOTIFS; **MEETING ABSTRACT**; MOLECULAR STRUCTURE
RN 74-79-3 (ARGININE)

L110 ANSWER 16 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1994:325944 BIOSIS
DN PREV199497338944
TI A genetic approach to the **generation** of antibodies with enhanced catalytic activities.
AU **Patten, Phillip A.**; Ullrich, Helle D.; Gray, Nathaniel S.;

Schultz, Peter G.
CS Dep. Chem., U.C. Berkeley, Berkeley, CA 94720 USA
SO Journal of Cellular Biochemistry Supplement, (1994) Vol. 0, No. 18D, pp. 195.
Meeting Info.: **Keystone Symposium on Antibody Engineering: Research and Application of Genes Encoding Immunoglobulins** Lake Tahoe, California, USA March 7-13, 1994
ISSN: 0733-1959.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Replication, Transcription, Translation *10300
Biophysics - Molecular Properties and Macromolecules *10506
Genetics of Bacteria and Viruses *31500
Immunology and Immunochemistry - General; Methods *34502
BC Enterobacteriaceae *06702
IT Major Concepts
Biochemistry and Molecular Biophysics; Genetics; Immune System (Chemical Coordination and Homeostasis); Molecular Genetics (Biochemistry and Molecular Biophysics)
IT Miscellaneous Descriptors
IMMUNOLOGIC METHOD; **MEETING POSTER**
ORGN Super Taxa
Enterobacteriaceae: Eubacteria, Bacteria
ORGN Organism Name
Escherichia coli (Enterobacteriaceae)
ORGN Organism Superterms
bacteria; eubacteria; microorganisms

L110 ANSWER 17 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1993:243705 BIOSIS
DN PREV199344116905
TI A genetic approach to the **generation** of antibodies with enhanced catalytic activities.
AU Lesley, Scott A.; **Patten, Phillip A.**; Schultz, Peter G. (1)
CS (1) Dep. Chemistry, Univ. California, Berkeley, CA 94720
SO **Proceedings of the National Academy of Sciences of the United States of America**, (1993) Vol. 90, No. 4, pp. 1160-1165.
Meeting Info.: **Meeting on Molecular Recognition** Washington, D.C., USA September 10-11, 1992
ISSN: 0027-8424.
DT Article
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Replication, Transcription, Translation *10300
Genetics of Bacteria and Viruses *31500
Immunology and Immunochemistry - General; Methods *34502
BC Enterobacteriaceae *06702
IT Major Concepts
Biochemistry and Molecular Biophysics; Genetics; Immune System (Chemical Coordination and Homeostasis); Molecular Genetics (Biochemistry and Molecular Biophysics)
IT Sequence Data
amino acid sequence; molecular sequence data; nucleotide sequence
IT Miscellaneous Descriptors
IMMUNOLOGIC METHOD
ORGN Super Taxa
Enterobacteriaceae: Eubacteria, Bacteria
ORGN Organism Name
Escherichia coli (Enterobacteriaceae)

ORGN Organism Superterms
bacteria; eubacteria; microorganisms